Report of the Expert Committee for the Selection and Inclusion of Medicines in the Pan American Health Organization Strategic Fund – July 2013

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

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Contents

Acronyms

ACCIb-CCIb	Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano
ACEi	Angiotensin Converting Enzyme inhibitor
ALLHAT	Antihypertensive and lipid-lowering treatment to prevent heart attack trial
ARB	Angiotensin Receptor Blockers
ATLAS	Adjuvant tamoxifen, longer against shorter
AZA	Azathioprine
BP	Blood pressure
CAPRIE	Clopidogrel versus aspirin in patients at risk of ischaemic events
CAS	Cyclosporine, azathioprine, and corticosteroid
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CMV	Cytomegalovirus
CNI	Calcineurin inhibitors
CNS	Central nervous system
CTD	Chlorthalidone
CVD	Cardiovascular disease
CYP	Cyclosporine
DFS	Disease-free survival
EML	Essential medicines list
EMLc	Essential medicines list for children
GRADE	Grading of recommendations assessment, development and evaluation
GODT	Global observatory on donation and transplantation
GVHD	Graft versus host disease
HCTZ	Hydrochlorothiazide
HER2+	Human epidermal growth factor receptor 2-positive
HF	Heart failure
HR	Hazard ratio
HS	Herpes Simplex
HSS/MT	Medicines and health technologies unit
ICER	Incremental cost-effectiveness ratio
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MMF	Mycophenolate mofetil
MRFIT	Multiple risk factor intervention trial

NCD	Noncommunicable disease
NICE	National Institute for Health and Care Excellence
NMH/ND	Noncommunicable Diseases and Disabilities Unit
NNT	Number needed to treat
NYHA	New York Heart Association
OR	Odds ratio
OS	Overall survival
PAD	Peripheral arterial disease
PAHO	Pan American Health Organization
pCR	pathologic Complete Response
PFS	Progression-free survival
QALY	Quality-Adjusted Life Year
RCIDT	Red/ Consejo Iberoamericano de Donación y Trasplantes
RCT	Randomized controlled trial
RR	Relative risk
sRL	Sirolimus
TAC	Tacrolimus
TAS	Tacrolimus, azathioprine and a corticosteroid
VKA	Vitamin K Antagonist
WHO	World Health Organization

Executive Summary

The inaugural meeting of the Expert Committee for the Selection and Inclusion of Medicines in the Pan American Health Organization Strategic Fund was held at the Headquarters of the Pan American Health Organization (PAHO) in Washington, D.C., on 17-18 July 2013.

Experts from the Region of the Americas where convened to provide recommendations to the PAHO Director for the potential inclusion of eight medicines in the Strategic Fund Medicine List. The names of the members of the Expert Committee and their corresponding declarations of interests are provided in the full report.

The Expert Committee reviewed applications for eight medicines for the treatment of noncommunicable diseases, such as cardiovascular disease and cancer, and immunosuppressive medicines used to prevent graft rejection after transplantation. The Committee evaluated the presented evidence regarding effectiveness, safety and cost in comparison to alternative treatments already present in the Strategic Fund Medicine List.

The Expert Committee issued the following recommendations to the PAHO Director:

- Include six medicines (chlorthalidone, clopidogrel, losartan, mycophenolate mofetil, tacrolimus and trastuzumab) in the Strategic Fund Medicine List
- Reject two medicines (lisinopril and sirolimus) in the Strategic Fund Medicine List

PAHO in its function as the secretariat of the Expert Committee prepared the medicine dossiers at the request of Member States and/or PAHO Technical Units. The product dossiers and a summary of the committee's evaluations are available in the full report.

The Committee worked exclusively on evaluating the applications for potential inclusion in the Strategic Fund Medicine List, which enabled PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the Essential Medicine List or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists. As a result, the recommendations issued by this Committee should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

List of Participants

Experts

Dr. Lisa Bero, Chair of Expert Committee, Professor, Department of Clinical Pharmacy, University of California, San Francisco, United States of America

Dr. Perla M. de Buschiazzo, Co-Chair of Expert Committee, Director, Centro Universitario de Farmacología (CUFAR), Facultad de Ciencias Médicas. Universidad Nacional de La Plata (UNLP), Medical Doctor, Full Professor of Pharmacology (Retired) and Extraordinary Professor of School of Medicine, UNLP, La Plata, Argentina

Dr. Facundo Garcia Bournissen, Associate Researcher, Argentine National Science and Technology Research Council (Consejo Nacional de Investigaciones Científicas y Técnicas – CONICET), Buenos Aires, Argentina

Dr. Carlos Alberto Cuello-Garcia, Director, Center for Evidence-Based Practice and Knowledge Translation, Tecnológico de Monterrey School of Medicine and Health Sciences, Monterrey, Mexico

Dr. Albin Chaves Matamoros, Director of Pharmacoepidemiology, Costa Rica Social Security, San Jose, Costa Rica

Dr. Edgard J. Narváez Delgado, Advisor, United Nations Population Fund, Managua, Nicaragua

Dr. Lenita Wannmacher, Associate Professor (Retired), Department of Pharmacology, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

Collaborators

The evidence presented in the product dossiers was obtained in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb), Barcelona, Spain.

The indications specified in the clinical questions presented for mycophenolate mofetil, sirolimus and tacrolimus are based on input from three PAHO Member States (Costa Rica, Ecuador and Uruguay).

This report and the medicine dossiers were prepared with the assistance of Alexandra Guta, during her internship with PAHO, under the supervision of the PAHO Medicines and Health Technologies (HSS/MT) Unit.

Declaration of Interests of Members of the Expert Committee for the Selection and Inclusion of Medicines in the PAHO Strategic Fund

Members reported the following interests

Dr. Lisa Bero reported being a member of the WHO Expert Committee for the Selection of Essential Medicines since 2005

Dr. Perla M. de Buschiazzo reported no conflict of interest

Dr. Facundo Garcia Bournissen reported no conflict of interest

Dr. Carlos Alberto Cuello-Garcia reported no conflict of interest

Dr. Albin Chaves Matamoros reported no conflict of interest

Dr. Edgard J. Narváez Delgado reported no conflict of interest

Dr. Lenita Wannmacher reported no conflict of interest

Introduction to the PAHO Strategic Fund and Expert Committee

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (hereinafter "PAHO Strategic Fund" or "Strategic Fund"), was created in 1999 by the Director of PAHO at the request of Member States of the Organization.

The main objective of this regional mechanism is to strengthen the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe and effective supplies at affordable prices obtained by leveraging the advantages of economies of scale. To accomplish this objective the Strategic Fund publishes a list of medicines available for procurement in name of the Organization's Member States. The list utilizes as a foundation the World Health Organization (WHO) Essential Medicines List (EML).

Recently, the Strategic Fund has received requests for Member States regarding medicines that are not included in the WHO EML. In response, the PAHO Director established an external committee to review requests for inclusion of medicines presently not listed in the WHO EML, and make recommendations to the PAHO Director, based on its objective and independent review and analysis.

The primary objective of this committee is to allow PAHO to implement a decision making process for selection of medicines based on quality, efficacy, safety and when available information regarding the value added in comparison to the medicine's cost. Recommendations will be based on reviews of evidence that

support the efficacy and safety of the presented medicines and will provide an analysis of the therapeutic and economic advantages with respect to the medicines already incorporated on the PAHO Strategic Fund Medicine List. The PAHO Director will review the Committee's recommendations and make a final decision for inclusion or otherwise into the PAHO Strategic Fund Medicine List.

The committee will work exclusively on requests to update the Strategic Fund medicine list, which will enable PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this Expert Committee should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

Applications for medicines for the treatment of noncommunicable diseases (chlorthalidone, clopidogrel, lisinopril, losartan and trastuzumab) where requested and supported by the PAHO Noncommunicable Diseases and Disabilities Unit (NMH/ND). The applications for immunosuppressive medicines used to prevent graft rejection after transplantation (mycophenolate mofetil, sirolimus and tacrolimus) where requested and supported by the Regional Advisor for Blood Transfusion and Organ Transplant from the PAHO Medicines and Health Technologies Unit (HSS/MT).

Applications where submitted to the Strategic Fund, which is housed within the HSS/MT Unit and functions as the secretariat of the Expert Committee. Staff from the Strategic Fund prepared the product dossiers with the corresponding evidence regarding efficacy, safety and cost of the requested medicine in comparison to alternative treatments already present in the Strategic Fund Medicine List. Additionally, the product dossiers contain information about the public health relevance of the medicine, the pharmacotherapeutic characteristics, the regulatory status of the product in the Region of the Americas and other relevant information.

The indications specified in the clinical questions for each product dossier were developed with input from the PAHO technical unit supporting the application. For the immunosuppressive medicines additional input was received from three Members States (Costa Rica, Ecuador and Uruguay). Prior to conducting the search of evidence, the proposed clinical questions where reviewed by the chair and co-chair of the Committee. The search of evidence for the developed clinical questions was conducted in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb). The evidence summaries contained the corresponding Grading of Recommendations Assessment, Development and Evaluation (GRADE), and when relevant, characteristics of the critically reviewed clinical trials.

Prior to the meeting all product dossiers where submitted to the Expert Committee members for review. The Committee consists of eight members; however, one expert withdrew prior to the meeting and did not submit any reviews. Each expert was assigned three dossiers, resulting in three expert reviews for five of the applications (chlorthalidone, losartan, lisinopril, sirolimus and tacrolimus) and due to the absence of the withdrawn expert, two expert reviews for three of the applications (clopidogrel, mycophenolate mofetil and trastuzumab).

PAHO compiled the reviews received for each application and circulated the consolidated reviews to all the members of the Committee. PAHO then communicated any comments received from the consolidated reviews to the original three experts.

The experts convened in person to review each application, present any additional evidence, obtain consensus on the Committee's recommendations and approve this report. Logistical issues prevented Dr. Carlos Alberto Cuello-Garcia from traveling to the USA and he participated via Elluminate, an online meeting platform utilized by PAHO.

General Items

1. Meeting Proceedings

The Expert Committee meeting took place at the Pan American Health Organization Headquarters in Washington, D.C., United States of America, on 17-18 July 2013. The meeting's attendants were the seven members of the Expert Committee, the Director, a.i., of the PAHO Health Systems and Services Department, regional staff of the PAHO Strategic Fund (the Committee Secretariat), the PAHO Regional Advisor on Rational Use of Medicines, the PAHO Regional Advisor for Technological Innovation for Health, the PAHO Regional Advisor for Blood Transfusion and Organ Transplants, the PAHO Regional Advisor for Vaccines and Biotechnological Products, the Director of the PAHO Procurement Department and other PAHO staff serving as observers.

The meeting was opened by Dr. James Fitzgerald, Director, a.i., of the Health Systems and Services Department, on behalf of the PAHO Director, Dr. Carissa Etienne, who supported the establishment of this Committee. The Secretariat provided an introduction to the Strategic Fund and a brief explanation of the purpose, the objectives and the methodology for the Committee. Each expert was asked to declare any real or potential conflicts of interest and then the Committee reviewed and made final recommendations for the eight applications. The recommendations have been provided to the PAHO Director who will make a final decision for inclusion or otherwise into the PAHO Strategic Fund Medicine List.

2. General Recommendations

The Committee commented that none of the received applications contained evidence supporting use in pediatric populations. The Committee recommended, when relevant, inclusion of pediatric therapies to assist Member States increase access to pediatric treatments based on evidence. The Committee requested applications with potential impact for both adult and pediatric populations be evaluated jointly.

Additionally, the Committee recommended applications with similar indications be reviewed together in one session.

The Committee recommended future applications include more rigorous and independent direct head to head comparisons, which include clinically relevant outcomes.

Applications

The committee reviewed and made recommendations for eight applications, which are presented in three therapeutic categories (cardiovascular, cancer and transplant and immunosuppression medicines). Unless otherwise indicated, the supporting evidence for efficacy, safety and costs, including the corresponding references, are available in the medicine dossiers (See Annexes). To support the evaluation of the applications, the Committee provided reviews of the dossiers, which included additional evidence for efficacy, safety and cost.

1. Cardiovascular Medicines

Cardiovascular disease is the leading cause of death globally. Hypertension represents the greatest risk factor and is responsible for 62% of strokes and 49% of ischemic heart disease. In Latin America, 18% of the adult population suffers from hypertension. The growing prevalence of hypertension and cardiovascular diseases in the Region clearly demonstrates the need for increased access to different pharmacological classes of medicines to optimize treatment and prevent further potential complications such as stroke, acute coronary syndrome, congestive heart failure, death, and others. In response to the increasing burden of cardiovascular disease, PAHO Member States approved the Regional Strategy to prevent and control noncommunicable diseases, which was approved as Resolution CSP28.R13 during the 28th Pan-American Sanitary Conference in September 2012 (*1-3*).

To assist Member States implement Resolution CSP28.R13, the PAHO Noncommunicable Diseases and Disabilities Unit (NMH/ND) submitted and supported applications of chlorthalidone, clopidogrel, lisinopril and losartan for inclusion in the PAHO Strategic Fund Medicine List.

Below is a summary of the Expert Committee's review of chlorthalidone, clopidogrel, lisinopril and losartan and their corresponding recommendations.

1.1 Chlorthalidone

The efficacy, safety and cost of chlorthalidone were reviewed compared to hydrochlorothiazide, the alternative treatment currently available in the PAHO Strategic Fund Medicine List, for two clinical indications (hypertension and heart failure).

The experts who reviewed this application were Dr. Lenita Wannmacher, Dr. Albin Chaves Matamoros and Dr. Facundo Garcia Bournissen.

- Efficacy evidence for hypertension and heart failure:

  The evidence results provided in the reviewed dossier for hypertension and heart failure were based on a systematic review, which included 9 Randomized Controlled Trials (RCTs) and network meta-analyses of 4 of those RCTs. The dossier suggests chlorthalidone (CTD) is considered superior to hydrochlorothiazide (HCTZ) in reducing the risk of cardiovascular events by 21% (4 RCTs, RR 0.79, 95% CI 0.72 to 0.88, P<0.0001) and of congestive heart failure by 23%(4 RCTs, RR 0.77, 95% CI 0.61 to 0.98; P=0.032). Additionally, this systematic review found no differences between the two compared diuretics in terms of all-cause mortality, and stroke (*4*).

However, the Committee provided additional information derived from various studies, including another Cochrane systematic review. This systematic review provided information on thiazide efficacy as a pharmacological class. It showed first-line low-dose thiazides (12.5-25mg) reduced mortality (RR=0.89; 95%CI: 0.83-0.96), stroke (RR= 0.63; 95%CI: 0.57-0.71), coronary heart disease (RR=0.84; 95%CI: 0.75-0.95) and cardiovascular events (RR= 0.70; 95%CI: 0.66-0.76). Other classes of medicines such as angiotensin conversion enzyme inhibitors and calcium channel blockers maybe considered as effective but are supported by less robust evidence. On the other hand, beta-blockers and high-dose thiazides are considered inferior to low-dose thiazides (*5*).

Specific to the efficacy of CTD versus HCTZ to reduce blood pressure, the systematic review provided in the dossier found no statistical difference between the two medicines. However, other studies such as retrospective cohorts, randomized control trials and meta-analyses cited by the Committee concluded CTD is superior in lowering blood pressure compared to equal or higher doses in mg of HCTZ. These studies state the difference is even greater in the night-time period, probably due to the differences in the duration of action between both drugs. The significance level of the effect varies among the listed studies (*6-9*).

Moreover, among other results presented by the Committee, a majority of follow-up studies demonstrated no significant long-term differences between CTD and other classes of antihypertensive medicines. For example, follow- up of ALLHAT trial showed a 5-year treatment with other antihypertensive agents such as amlodipine or lisinopril was not superior to CTD in regards to all-cause mortality, end stage renal disease and prevention of cardiovascular events after 9 years (*10*). Also, data on mortality obtained after an 8.9 years follow-up of patients that developed new-onset heart failure during the randomized phase of ALLHAT trial showed all-cause mortality was similar across treatment groups (CTD, lisinopril, and amlodipine) (*11*). As a final point, follow-up results highlighted the importance of adequate blood pressure control in the prevention of long-term complications such as cardiovascular death, heart failure and end stage renal disease.

In conclusion, although some of the aforementioned studies provided by the experts are not comparing CTD directly to HCTZ, they demonstrate the advantage of CTD over other antihypertensive agents or placebo regarding cardiovascular outcomes, mortality or blood pressure control, which supports the use of this diuretic in the treatment of hypertension.

Less data was available for the treatment of heart failure; however, the overall available evidence established the superiority of CTD over HCTZ regarding mortality rate, prevention of cardiovascular events, potential to lower blood pressure and the risk of congestive heart failure.

- Safety evidence for hypertension and heart failure:

In terms of safety, the available evidence provided in the dossiers based on a retrospective population-based cohort study showed CTD had a higher risk of hospitalizations due to hypokalemia (adjusted HR 3.06 (CI 95%, 2.04 to 4.58)). and hyponatremia (adjusted HR 1.67 (CI95% 1.25 to 2.23)) compared to HCTZ (*12*).

Additionally, analyses provided by the Committee show CTD is responsible for a higher increase of laboratory values such as glucose and urates and for a higher rate of electrolyte disturbances (hypokalemia, hyponatremia, hypocalciuria). Analyses of ALLHAT trial data demonstrated CTD had a greater risk of developing fasting glucose levels higher than 125mg/dl (6.9mmol/l) compared to other antihypertensive treatments (*13*). A retrospective cohort analysis of MRFIT trial showed CTD was responsible for higher uric acid levels (P<0.0001) compared with HCTZ (*14*). The same MRFIT study also showed CTD had lower potassium than HCTZ(P=0.0003), a clinical outcome also supported by a retrospective observational

study showing a decrease in serum potassium in patient on CTD 25mg daily versus HCTZ 25mg daily (P = 0.001) without significant difference in severe hypokalemia or arrhythmia (*15*).

Nonetheless, increases in glucose or decrease in potassium are not necessarily correlated with the corresponding diseases or outcomes such as diabetes mellitus or arrhythmias and remain clinically non-significant in the majority of studies. Also, in the discussion, the Committee suggested that the potential clinical outcome of hospitalization associated to hypokalemia and hyponatremia can be avoided with the use of potassium sparing diuretics (amiloride, triamterene) in combination with thiazides.

The overall safety profile of CTD is considered acceptable with few clinically significant outcomes.

- Cost:

Regarding cost studies, no relevant cost effectiveness studies or economic evaluations were found that compared different types of diuretics such as CTD and HCTZ. One publication reported data on cost-effectiveness of CTD, amlodipine and lisinopril as first line treatments for hypertension, based on the data from ALLHAT trial. It showed that compared to amlodipine and lisinopril, CTD was in all cases the least expensive medicine (on average US$4,802 less than amlodipine, and US$3,700 less than lisinopril). It concluded that initial treatment with CTD was less expensive than the two other alternatives ([16]).

Additionally, the Committee discussed the use of thiazide-type diuretics in the health system of Costa Rica. Dr. Chaves indicated that CTD is currently not available in the national market and the cost of monthly treatment of HCTZ is US$0.022, which represents a more cost-effective treatment when compared to CTD.

- Additional comments discussed at meeting:

  - Additional comments were brought up by the Committee according to the presented evidence regarding heart failure. The Committee mentioned heart failure was often a consequence of hypertension and was considered as an outcome in various studies more than a condition required for patient inclusion in trials.
  - It was observed that there is a lack of head-to-head comparisons of CTD and HCTZ or other standard antihypertensive therapies in patients with heart failure. The majority of studies were conducted in patients with hypertension.
  - The Committee discussed the adequate presentation and dosage of CTD to be considered if the medicine is included on the Strategic Fund Medicine List. The evidence provided by the experts reiterated the need to make available lower dosages as treatment is incremental and not recommended to start with 50 mg. Additionally, the Committee noted that 50mg dose was not included in any of the reviewed studies evaluating hard outcomes and the evidence supports lower dosage (12.5mg & 25 mg).

- Recommendation:

In the light of all analyzed studies and presented evidence, the Committee concluded there is sufficient evidence supporting the benefits of CTD in the treatment of hypertension with an acceptable safety and an affordable cost and recommended the inclusion of CTD in the Strategic Fund Medicine List.

The expert Committee agreed there is presently not enough evidence to support inclusion of CTD for treatment of heart failure and rejected this indication.

Results from analyzed studies suggest CTD is at least as effective as HCTZ to reduce mortality, morbidity, cardiovascular outcomes and lower blood pressure in hypertensive patients. However, studies demonstrate low doses of 12.5mg and 25mg should be prioritized as there are significant concerns related

to patient safety when treatment begins with 50mg. Hence, the Committee has agreed to include only the 12.5mg and 25mg CTD dosage in the Strategic Fund Medicine List. The CTD 50mg presentation has been rejected based on safety evidence provided by the experts.

Additionally, several clinical guidelines support the use of thiazide diuretics as a first-line therapy for the treatment of hypertension without necessarily favoring one diuretic over the other. The Committee believes availability of a thiazide-like (CTD) in the Strategic Fund Medicine List will allow physician to tailor treatment to the specific needs of the patients.

In conclusion, the benefit harm ratio of CTD and the reviewed evidence support the recommendation for inclusion of CTD 12.5mg and 25mg for the treatment of hypertension in the Strategic Fund in order to increase access for Member States.

1.2 Clopidogrel

Clopidogrel is a platelet aggregation inhibitor, or antiplatelet, and there is no alternative of the same pharmacological class available in the PAHO Strategic Fund Medicine List; however acetylsalicylic acid is an alternative present on the WHO EML. Therefore, the Committee reviewed clopidogrel used as a single agent or in combination with aspirin versus aspirin or warfarin, dependent on the indication. The Committee reviewed clopidogrel for the prevention of:

1. Atherothrombotic events in adults when indicated for secondary prevention of myocardial infarction, stroke or peripheral arterial disease
2. Atherothrombotic events in adults with ST segment elevation or without ST segment elevation acute coronary syndrome
3. Prevention of atherothrombotic and thromboembolic events in adults with atrial fibrillation

The experts who reviewed this application were Dr. Carlos Alberto Cuello-García, and Dr. Albin Chaves Matamoros.

- Efficacy evidence results for clopidogrel compared to aspirin:

  Based on the Cochrane systematic review and a health technology assessment, there is high quality evidence to demonstrate that in adults with previous myocardial infarction (MI), stroke or peripheral arterial disease (PAD), clopidogrel reduces the risk of MI compared to aspirin (OR 0.80; 95%CI 0.68 to 0.94). No differences were observed in the rate of mortality for any cause (OR 0.98; 95%CI 0.87 to 1.10) or strokes (OR 0.91; 95%CI 0.80 to 1.04) (*17,18*).

- Efficacy evidence results for clopidogrel + aspirin compared to aspirin alone:

  The evidence was retrieved from a Cochrane systematic review aimed at assessing the benefit and harm of adding clopidogrel to standard aspirin therapy for preventing cardiovascular events in patients at high risk of cardiovascular disease (CVD) and those with established CVD. The results showed that in patients with acute non-ST segment coronary syndromes, the combination of clopidogrel and aspirin reduced the rate of cardiovascular events compared with aspirin alone (OR 0.84; 95%CI 0.77 to 0.93; high quality evidence) (*19*).

  In patients with ST-elevation myocardial infarction, the combination of clopidogrel and aspirin reduced the rate of major coronary events compared to aspirin alone (OR 0.90; 95%CI 0.85 to 0.96; high quality evidence), but no statistical significant difference was observed in terms of mortality (*20*).

The results also demonstrated that in patients with established CVD and at high risk of CVD, the combination of clopidogrel and aspirin did not show a statistically significant difference in the rate of cardiovascular events compared to aspirin alone (OR 0.92; 95%CI 0.81 to 1.04; moderate quality evidence) (*19*).

- Efficacy evidence results for clopidogrel + aspirin compared to warfarin:

The evidence was retrieved from a Cochrane systematic review aimed at assessing the effects of long-term treatment with oral anticoagulants compared with antiplatelet therapy in the rate of major vascular events in patients with non-valvular atrial fibrillation, without a history of stroke or transient ischemic attack ([21]).

Only one trial included in the review compared the combination of clopidogrel and aspirin with a vitamin K antagonist therapy (warfarin). The results showed that in patients with atrial fibrillation, treatment with vitamin K antagonist (VKA) resulted in a statistically significant reduction of the risk of stroke (OR 0.60; 95%CI 0.44 to 0.81), particularly in the rate of ischemic stroke (OR 0.46; 95%CI 0.33 to 0.65), and in the rate of systemic (non-CNS) embolisms (OR 0.32; 95%CI 0.14 to 0.72) compared with the combination of clopidogrel and aspirin (*22*).

However, no differences was noted between the combination of clopidogrel + aspirin and VKA therapy in the rate of myocardial infarction (OR 0.63; 95%CI 0.38 to 1.06), all-cause mortality (OR 0.98; 95%CI 0.78 to 1.23) or vascular death (OR 0.89; 95%CI 0.68 to 1.15) (*22*).

- Safety evidence for all indications:

The safety evidence presented in the dossier was based on three Cochrane systematic reviews and reported data on major and serious adverse events such as, intracranial and extracranial hemorrhage, neutropenia, thrombocytopenia and gastro-intestinal bleeding.

The results stated in the review of evidence comparing clopidogrel to aspirin in patients with previous MI, stroke or PAD, showed that treatment with clopidogrel was associated with an increase of skin rashes compared to aspirin (OR 1.32; 95%CI 1.17 to 1.50; high quality evidence). However, clopidogrel and aspirin did not differ in the rate of extracranial bleeding (OR 1.02; 95%CI 0.92 to 1.12; moderate quality evidence), the rate of severe gastro intestinal hemorrhages (OR 0.69; 95%CI 0.48 to 1.00; moderate quality evidence), rate of neutropenia (OR 0.63; 95%CI 0.29 to 1.36; moderate quality evidence) and rate of thrombocytopenia (OR 1.00; 95%CI 0.57 to 1.74; moderate quality evidence) (*17,18*).

In patients with ST-elevation acute coronary syndrome and patients with established CVD, clopidogrel and aspirin compared to aspirin alone, showed no statistically significant increase in the risk of major bleeding (OR 1.07; 95%CI 0.86 to 1.34; ST-elevation and MI, high quality evidence; OR 1.25; 95%CI 0.97 to 1.63; established CVD, moderate quality evidence). However, in patients with non-ST elevation acute coronary syndrome, clopidogrel and aspirin compared to aspirin alone increased the risk of major bleedings (OR 1.39; 95%CI 1.14 to 1.70; high quality evidence) (*19,20*).

In patients with atrial fibrillation, the results of the Cochrane systematic review evaluating clopidogrel and aspirin compared to warfarin showed that there were no differences in the risk of major extracranial bleeding (OR 0.80; 95%CI 0.58 to 1.09; moderate quality evidence) or the risk of intracranial hemorrhage (OR 1.85; 95%CI 0.93 to 3.71; moderate quality evidence) between the combination of clopidogrel + aspirin and the VKA therapy (warfarin) (*21*).

- Cost:

The cost evidence presented in the dossier was based on two economic evaluations regarding the cost effectiveness of clopidogrel used for the requested indications. An economic evaluation based on CAPRIE's

trial data showed that clopidogrel was a cost-effective alternative to aspirin as secondary prevention of cardiovascular or cerebrovascular events in patients with previous MI, ischemic stroke or previously diagnosed with peripheral arterial disease. The Study used a Morkov model and was based on a two year period with a perspective of German third-party payers (*23*).

Another economic evaluation demonstrated that the combination of clopidogrel and aspirin was a cost-effective treatment for patients with non-ST segment elevation acute coronary system, and that shorter treatment durations for clopidogrel might be more cost-effective in patients at low risk. The study synthesized a health technology assessment that performed a cost-utility analysis with the perspective of the UK National Health System (*24,25*).

No economic evaluations of clopidogrel and aspirin combination versus aspirin were found in patients with established CVD, or ST-segment elevation acute coronary syndrome. Additionally, no studies were presented to assess the cost-effectiveness of antiplatelet combination therapy (clopidogrel and aspirin) compared to VKA therapy (warfarin) in patients with atrial fibrillation.

The information supported by the retrieved economic analyses show that, for some indications, the use of clopidogrel can be considered a cost-effective alternative to aspirin.

In addition to the cost-effectiveness studies presented in the dossier, information regarding the price difference of clopidogrel was provided by Dr. Chaves, who stated that the variance in unit price among different countries of the Region is an important issue to consider. Dr. Chaves noted that in the United States, a tablet of clopidogrel 75mg can be procured at US$0.20/unit, and in Costa Rica, clopidogrel 75mg (from the innovator) can be procured at US$1.10/unit. This shows that in Costa Rica, a country with a per-capita income significantly inferior to the US, the daily treatment cost with clopidogrel 75 mg is approximately 5.5 times higher than in the US.

- Additional comments discussed at meeting:
  - The Committee noted clopidogrel is widely used in the region for many indications that have not been supported by adequate efficacy and safety data. While clopidogrel does present therapeutic advantages for a very specific indication (see Recommendation) it is critical to ensure PAHO works with Member States in developing treatment guidelines and protocols that are evidenced based and promote the rational use of clopidogrel.
  - The Committee only considered economic data for the indication recommended by the Committee.
  - The Committee noted the value added clopidogrel may provide for patients with allergies to aspirin.
- Recommendation:

  Based on the available evidence, the Committee recommended the inclusion of clopidogrel 75 mg tablets as an antiplatelet therapy in the Strategic Fund Medicine List for prevention of atherothrombotic events in adults with non-ST segment elevation acute coronary syndrome and recommended rejecting the inclusion of clopidogrel as an antiplatelet therapy for the prevention of the following indications:

  1. Atherothrombotic events in adults when indicated for secondary prevention of myocardial infarction, stroke or peripheral arterial disease
  2. Atherothrombotic events in adults with ST segment elevation acute coronary syndrome
  3. Atherothrombotic and thromboembolic events in adults with atrial fibrillation

The Committee concluded that the efficacy, safety and cost-effectiveness of clopidogrel vary among the requested indications and that clopidogrel as a single agent or in combination with aspirin is superior to aspirin for very specific outcomes and the superiority of clopidogrel cannot be generalized among all requested indications.

The benefit harm ratio is variable and the prescription of this medicine should be individualized and performed by health practitioners with medical expertise and capacity of assessing potential benefits. As a result, if Clopidogrel is included, its use should follow clinical practice guidelines based on the latest evidence available, considering the strength of those recommendations on an individual patient-basis.

When added to aspirin, clopidogrel proved to be effective in reducing cardiovascular events in patients with non-ST elevation acute coronary syndrome. The combined therapy also increased the risk of major bleeding compared to aspirin alone in patients with non-ST segment elevation acute coronary syndrome.

Clopidogrel showed to be cost-effective when added to aspirin in patients with non-ST segment elevation acute coronary syndrome.

In conclusion, the Committee agreed the presented evidence regarding efficacy, safety and cost is sufficient to include clopidogrel, as an antiplatelet therapy, in the Strategic Fund Medicine List for the prevention of atherothrombotic events in adults with non-ST segment elevation acute coronary syndrome. However, the Committee reiterated the use of this medicine should be further guided by clinical practice guidelines to ensure rational use guided by the most recent evidences.

1.3 Lisinopril

The efficacy, safety and cost of lisinopril were reviewed compared to enalapril, the alternative treatment currently available in the PAHO Strategic Fund Medicine List, for two clinical indications (hypertension and heart failure).

The experts who reviewed this application were Dr. Edgard J. Narváez Delgado, Dr. Perla M. de Buschiazzo and Dr. Lenita Wannmacher.

- Efficacy evidence for hypertension and heart failure:

The evidence results provided in reviewed dossier for hypertension and heart failure were not based on systematic reviews. Data was obtained from the few and outdated available head-to-head comparison trials of lisinopril and enalapril for the mentioned indications. The quality of the evidence was considered very low to low, depending on the outcome. To complement the dossier, experts provided input from a variety of studies comparing lisinopril to enalapril, placebo or other antihypertensive treatments.

For hypertension, the evidence presented in the dossier was based on 5 clinical trials that performed head-to-head comparison between the two treatments. Pooled results from all trials concluded similar efficacy of both medicines in lowering blood pressure; however, the studies included a small number of patients and lasted for short periods of time. Also, relevant outcomes such as mortality, prevention of cardiovascular events or effects in patients at high-cardiovascular risk or with various co-morbidities were not addressed in the trials (*26-30*).

The Committee addressed these shortcomings by providing additional evidence comparing lisinopril to standard treatments for these outcomes. The following highlights the supplementary evidence in terms of efficacy that was provided by the Committee:

- Two Cochrane reviews evaluated ACEi versus placebo regarding efficacy in both systolic and diastolic blood pressure following hypertensive emergencies and found equivalent antihypertensive efficacy among the different classes. The BP lowering effect of ACEi was modest. No ACEi was considered superior to another. No difference in mortality and morbidity (*31,32*).
- ALLHAT trial: Lisinopril demonstrated higher systolic and diastolic blood pressure throughout the trial (compared to amlodipine and CTD); lisinopril showed less antihypertensive effect in black patients (compared to CTD); lisinopril had less effective blood pressure control (compared to amlodipine) (*33*).
- ALLHAT Post-trial results (8-13 years later): No significant differences in cardiovascular mortality (amlodipine or lisinopril vs. CTD); stroke mortality was higher with lisinopril (compared with CTD); ACEi are not superior for the long term prevention of major cardiovascular complications of hypertension (compared to diuretics) (*34*).
- Small crossover trial (n = 34): Lisinopril is superior to enalapril to reduce blood pressure ($P < 0.009$) (*35*).
- RCT (n=40): Lisinopril is superior in lowering BP (systolic and diastolic), mean blood pressure and pulse pressure compared to placebo after acute ischemic stroke, at day 14 ($P < .01$) (*36*).
- Meta-analysis (20 clinical trials): ACEi resulted in significant reduction in all-cause mortality in patients with hypertension compared to AT1 receptor blockers (ACEi used in 7 trials and lisinopril and enalapril in 4 trials). 7 trials demonstrated 10% reduction in all-cause mortality and 12% reduction in CV deaths (trials controlled with placebo, thiazide-type diuretic, atenolol or calcium blockers) (*37*).
- ALLHAT trial: No difference between treatment groups for primary outcome as coronary heart disease (CHD) or non-fatal myocardial infarction (MI) and all-cause mortality (lisinopril vs. amlodipine or lisinopril vs. CTD) (*38*).
- The use of ACEi in black patients is not recommended as a first line-therapy for antihypertensive therapy. Experts provided studies with additional information on the use of this pharmaceutical class in black patients. A Cochrane systematic review of 30 trials including 20,006 black patients and considering 8 classes of antihypertensive agents showed no difference in mortality and morbidity outcomes in the treatment of black patients; however, it states agents differ in their ability to reduce blood pressure where ACEi are the least effective in black adults (*39*).

For heart failure, the evidence provided in the dossier is based on two clinical trials, which failed to show any differences between lisinopril and enalapril with regards to various outcomes such as congestive heart failure symptomatology, left ventricular ejection fraction, heart rate, and others (*40,41*). To compensate for the lack of evidence, the Committee included in the discussion results from other studies comparing lisinopril or enalapril compared to placebos or other standard therapies. The following highlights the supplementary evidence in terms of efficacy that was provided by the Committee:

- Classical studies (CONSENSUS, SOLVD, ATLAS, ACE-Inhibitor Myocardial Infarction Collaborative Group) (*42-45*). ACEi reduced mortality and morbidity in patients with severe NYHA heart failure and in a minor degree in patients with low to moderate HF (*42*). Addition of enalapril to conventional therapy reduced rate of hospitalizations for heart failure, incidence of myocardial infarction and angina pectoris in patients with CHF with low ejection fractions (*43*). High-dose lisinopril lowered risk of death or hospitalization in patients with heart failure (compared to low-dose lisinopril) (*45*).

- ALLHAT trial (Post-trial follow-up 8.9 years): Post-heart failure all-cause mortality was similar across treatment groups (amlodipine and lisinopril compared with CTD) and no differences observed between reduced rejection fraction and preserved rejection fraction treatment arms (*11*).
- ATLAS study: Lisinopril at high doses (33.2 mg/day), plus beta blockers, plus digoxin, was associated with incrementally greater reductions in morbidity and mortality than low dose ACEi (*46*).

The aforementioned studies present results that can demonstrate the efficacy of ACEi, and sometimes lisinopril in particular, in comparison to other standard treatments of adult patients with hypertension and/or heart failure to reduce blood pressure, mortality, morbidity or cardiovascular events. Conclusions of lisinopril's effectiveness can be derived from these results; however, the strength of the evidence is variable from one study to another.

The lack of comparative studies with enalapril highlights the importance of additional evidence and larger studies performed on longer periods in order to compare efficacy among two medicines of the same class. These studies should assist in determining which of the two treatments is superior in reducing blood pressure and reducing clinical outcomes in the long-term for patients with hypertension and heart failure.

- Safety evidence for hypertension and heart failure:

The safety evidence presented in the dossiers was based on few clinical trials with a small number of patients and performed on short periods of time. The safety profile for lisinopril and enalapril are very similar. No statistical difference among adverse events was found in the presented results. Some of the minor adverse events having occurred in trials are cough, dizziness, headache, dyspepsia and asthenia. The rate of withdrawal due to adverse events remained statistically not significant when lisinopril was compared to enalapril. Additional studies provided by the experts indicate hypotension, hyperkalemia and cough were reported in patients receiving lisinopril or other ACEi (*47,48*).

Supplementary safety issues regarding the use of lisinopril in specific populations were also considered. Lisinopril and other ACEi can cause fetal toxicity and neonatal mortality; therefore, must be avoided during pregnancy. The use of ACEi is not recommended during breast-feeding.

Overall, the safety profile of lisinopril and enalapril are very similar and safety concerns are referred to the ACEi class in general rather than to one medicine in particular.

- Cost:

Presently, there is insufficient and inadequate evidence to compare the cost-effectiveness of lisinopril to enalapril or another ACEi. The only study available supporting the comparison of the two ACE inhibitors in the reviewed dossier is a cost-effectiveness study of a voluntary program including 177 patients that switched enalapril to lisinopril therapy in patients with essential hypertension. The study concluded net saving ranged from US$85 to US$110 per patient converted from enalapril to lisinopril (*49*).

According to the experts' reviews, ACEi should not be used as a first-line therapy in hypertension. Other treatments such as diuretics are less expensive and as effective and safe. A cost-effective analysis on data of ALLHAT trial showed initial treatment with CTD (thiazide-diuretic) was always less expensive than amlodipine (calcium channel blocker), and lisinopril (ACEi). Lisinopril provided fewer life-years than CTD despite a higher cost (*50*).

Considering the use of ACEi in heart failure, some trial results demonstrate ACEi reduced heart failure and hospitalizations. ATLAS trial showed that high doses of lisinopril were associated with a reduction in the number of hospitalizations for heart failure and with a statistically non-significant reduction in

mortality, if compared to low-dose lisinopril. An economic analysis of the trial demonstrated cost savings from fewer heart failure hospitalizations offset higher ACEi costs in high-dose treatments (*51*).

The results illustrate that the cost benefit of lisinopril can vary among the indications and can be influenced by the doses used. Lisinopril does not appear as the most cost-effective option in the treatment of hypertension, if compared to other existing treatments. In heart failure, use of high-dose lisinopril showed that reduction in hospitalization rates enables cost savings. However, the available evidence comparing lisinopril to enalapril is not strong enough to conclude lisinopril is more cost-effective. It is important to note that lisinopril has a higher cost than enalapril, which is already included in the PAHO Strategic Fund Medicine List.

- Additional comments discussed at meeting:
  - The Committee requested the Secretariat work with the PAHO NCD technical unit to identify how many countries in the Region have incorporated lisinopril as an ACEi in their national list. The Committee requested information for countries that have both enalapril and lisinopril and countries that have only lisinopril in their essential medicine list.
- Recommendation:

  Based on the available evidence, the Committee recommended rejecting the inclusion of lisinopril in the Strategic Fund Medicine List for treatment of adult hypertension and heart failure considering the provided evidence did not support the superiority of lisinopril' s efficacy and safety compared to enalapril.

  For hypertension treatment reliable systematic reviews and randomized controlled trials did not show that lisinopril was superior compared to other ACEi, specifically for the compared medicine (enalapril). The Committee noted enalapril, which is already in the Strategic Fund Medicine List, and lisinopril share a similar benefit risk ratio and lisinopril has a higher cost. Hence, the inclusion of lisinopril for treatment of hypertension is not justified.

  For heart failure treatment, there is evidence supporting ACEi efficacy in reducing mortality and morbidity in patients with heart failure. However, considering that differential effects among ACEi are not supported by strong evidence and that enalapril, an alternative already available in the Strategic Fund Medicine List, is less expensive, there is no need for including lisinopril in the List.

1.4 Losartan

Losartan is an antihypertensive medicine from the angiotensin receptor blockers (ARB) pharmacological class. The use of ARBs as a pharmacotherapeutic class in the management of hypertension and heart failure is supported by international clinical practice guidelines based on the most recent evidence. The evidence reviewed by the Committee compared losartan to valsartan, another ARB. The Committee reviewed losartan for three clinical indications (hypertension, hypertension in type II diabetic patients with proteinuria and heart failure).

The experts who reviewed this application were Dr. Lisa Bero, Dr. Edgard J. Narváez Delgado and Dr. Facundo Garcia Bournissen.

- Efficacy evidence for all indications:

  The evidence summary presented in the reviewed dossier is of low or very low quality as only one systematic review was available to support the requested indications.

In hypertension, no head-to-head comparisons were performed. A 2008 systematic review indirectly assessed the comparative efficacy of valsartan and losartan to reduce systolic and diastolic blood pressure and found valsartan was more effective to reduce blood pressure at higher doses than losartan (*52*).

In hypertensive type II diabetic patients with proteinuria, only one head-to-head comparison trial was found as no systematic reviews were available. The results presented no significant differences in regards to the compared efficacy to reduce blood pressure of losartan and valsartan treatments (*53*).

In patients with heart failure, a Cochrane systematic review found insufficient data to conclude a difference in mortality as the main outcome between compared medicines. No head-to-head comparisons were performed but the data retrieved from a USA retrospective database analysis demonstrated similar effectiveness in reducing mortality in congestive heart failure patients for losartan versus valsartan. However, a Canadian retrospective population-based study showed that valsartan was associated with better survival rates than losartan (adjusted HR 0.63; 95%CI: 0.51 to 0.79). Nonetheless, the overall results were insufficient to conclude a difference in mortality (*54*).

To support the review of losartan, the Committee provided additional evidence comparing the efficacy of two different ARBs in hypertension and heart failure. The Committee commented that, based on other studies where ARBs are compared to ACEi, it can be concluded that ARBs seem as effective as ACEi in reducing mortality and major cardiovascular events, but are often more expensive. Angiotensin receptor blockers are therefore considered second line therapy, after ACEi, for specific indications, and are often reserved for patients for whom ACEi are indicated but not tolerated (*37,55*).

A meta-analysis of studies compared losartan and candesartan head-to-head for hypertension but was unable to find head-to-head comparison studies in the treatment of heart failure. The results showed a small advantage of candesartan in reducing systolic blood pressure compared to losartan; however, the authors concluded the difference in reducing blood pressure in hypertensive patients was of questionable significance. No robust evidence supported the superiority of candesartan over losartan in the treatment of heart failure. As a result, losartan was adopted as the ARB of choice by UK National Health Service mostly on the basis of cost (*56*).

Another systematic review comparing candesartan and losartan demonstrated candesartan was superior to losartan in reducing blood pressure and seemed to cause fewer serious adverse events. Candesartan demonstrated better control of blood pressures and higher response rates than losartan (*57*).

Moreover, studies often compare ARBs to ACEi, an antihypertensive class of medicines generally used for the same specific indications. As an example, the study ONTARGET evaluated telmisartan (ARB) compared to ramipril (ACEi) and concluded similar efficacy in lowering blood pressure and prevention of cardiovascular events in high-risk diabetes and vascular disease patients. No studies comparing losartan and ACEi were conducted (*58*).

In conclusion, the lack of data from head-to-head comparison studies of losartan and valsartan in the reviewed indications of hypertension and heart failure limit the applicability of the available evidence to decide if any of these ARBs can be preferred over the other in terms of efficacy. Other available studies comparing losartan with other ARBs (candesartan) failed to demonstrate the superiority of losartan in most outcomes.

- Safety evidence for all indications:

In relation to compared safety, the results presented in the reviewed dossier were not extensive. The data from studies included in the Cochrane Systematic Review that assessed the safety of ARBs (including

losartan and valsartan) in patients with hypertension showed that all doses ARBs resulted in a reduction in withdrawal due to adverse events compared with placebo (RR of withdrawal 0.68; 95%, CI 0.54 to 0.87). Other important outcomes related to cardiovascular risk reduction were omitted such as heart failure, cardiovascular death, fatal or non-fatal myocardial infarction or stroke (*59*).

To support the safety review of losartan, the Committee presented additional studies. One study comparing losartan to candesartan, another ARB, demonstrated no difference in the rate of common adverse events, but showed a higher incidence of serious adverse events for losartan compared to candesartan (*56*). Also, in comparison with ACEi, ARBs resulted in a decrease in cough, less withdrawals due to adverse events and less incidence of angioedema compared to ACEi; however, the study did not review individual medicines within each class (*60*). This information allows for a comparison of the safety of losartan within its pharmaceutical class or compared to another antihypertensive class used for similar indications, but it does not provide sufficient information to compare losartan to valsartan. The study also demonstrates the superiority of ARBs in the rate of adverse events and tolerance compared to ACEi, but cannot prove the superiority of losartan within this class.

The Committee also noted losartan, or any other ARB, should be avoided during pregnancy, especially during the second and third semester, used with caution in women with child bearing potential, in patients at risk of hyperkalemia or in patients with bilateral renal artery stenosis.

- Cost:

In terms of cost studies, the available evidence provided in the reviewed dossier states only one cost-effectiveness study comparing generic losartan and valsartan for the treatment of adult hypertension. This study found valsartan to be cost-effective compared with switching to generic losartan, from a third-party perspective. The overall quality of the study was adequate; however, assumptions were limited due to lack of data (*61*).

No relevant economic evaluations assessing the cost-effectiveness of losartan and valsartan were retrieved in patients with hypertension associated with type II diabetes and proteinuria or heart failure.

To support the review of losartan, the Committee presented an example of a comparative cost-effectiveness study of branded candesartan and generic losartan in the management of hypertension and heart failure to demonstrate that although candesartan reduced blood pressure to a greater extend when compared with losartan, the difference was unlikely to be cost-effective. No robust evidence supported the use of candesartan over losartan in heart failure. As a result, the UK National Health System decided to choose generic losartan due to its lower cost in comparison to candesartan (*56*).

- Additional comments discussed at meeting:

  - The Committee addressed the limitations and difficulties faced in regards to the formulation of the clinical questions aiming at comparing two ARBs, losartan to valsartan. The Committee suggested that further reviews for potential inclusion of medicine belonging to a new pharmaceutical class be compared to an existing alternative class of medicine already included in the Strategic Fund Medicine List.

- Recommendation:

Based on the reviewed evidence for efficacy and safety, the Committee recommended the inclusion of losartan 25, 50 and 100 mg tablets for treatment of adults with hypertension for those patients in whom ACEi are indicated but not tolerated, specifically due to the presence of adverse events (mainly cough), including the sub-population of hypertensive patients associated with type II diabetes with proteinuria.

Due to the complications encountered with the clinical question posed to the Committee, the Committee concluded there was not enough evidence available to the Committee to include losartan for heart failure.

The Committee noted that the reviewed evidence did not allow for determining losartan as superior to valsartan, or other ARBs. However, the decision to include losartan was made as losartan was the first ARB available in the market and more studies are available for losartan in comparison to other ARBs. Additionally, generic presentations of losartan are available in the international market and the product is already registered throughout the Region.

2. Cancer Medicines

In the Region of the Americas, cancer, the second leading NCD, represents a major health and economic concern, particularly due to the increasing incidence and the high costs of treatment. In Latin America, an estimated 114,900 women are diagnosed with breast cancer every year and there are approximately 37,000 deaths yearly caused by the disease. Breast cancer is considered the most common cancer among women and having the highest death rates in Latin America. In response to the increasing burden of cancer, PAHO Member States approved the Regional Strategy to prevent and control noncommunicable diseases, which was approved as Resolution CSP28.R13 during the 28th Pan-American Sanitary Conference in September 2012 (*1*,*2*,*62*).

To assist Member States implement Resolution CSP28.R13, the PAHO Noncommunicable Diseases and Disabilities Unit (NMH/ND) submitted and supported the application of trastuzumab for inclusion in the PAHO Strategic Fund Medicine List.

Below is a summary of the Expert Committee's review of trastuzumab.

2.1 Trastuzumab

The Committee reviewed evidence of trastuzumab utilized as a single agent or in combination therapy for two indications (treatment of adult women with HER2+ early stage breast cancer and HER2+ advanced metastatic stage breast cancer). The use of trastuzumab for HER2+ early and advance metastatic breast cancer is supported by international clinical practice guidelines based on the latest evidence.

Unlike the other applications reviewed by the Committee, the evidence presented to the experts was compiled by different sources for each indication.

In January 2013, trastuzumab was submitted for inclusion in the WHO Essential Medicine List (EML) for the treatment of adult women with HER2+ early stage breast cancer. The Committee reviewed the evidence presented by WHO for early stage breast cancer. The WHO Selection Committee convened in Geneva in April 2013 and WHO has decided to defer a decision on trastuzumab for HER2+ early stage breast until this application undergoes an urgent review. The urgent review called by WHO will be a process similar to that used for the cytotoxic and adjuvant medicines section in the EML for children (EMLc). This process requires the identification of the treatable, public health relevant tumors in adults, and the identification of the medicines required to treat those tumors, considering a stepwise development of cancer care systems in the overall context of health system development. The WHO Expert Committee noted the strong evidence in support of trastuzumab but deferred the final decision and its potential inclusion until a further review of the section of cytotoxic and adjuvant medicines is completed (*63*).

For the treatment of HER2+ advanced metastatic breast cancer the Committee reviewed a product dossier prepared by PAHO.

The experts who reviewed this application were Dr. Lenita Wannmacher, Dr. Albin and Chaves Matamoros.

- Efficacy evidence for early stage HER2+ breast cancer:

  As the reviewed dossier focused on the evidence supporting use in HER2+ advanced metastatic breast cancer, the Committee provided additional references, mainly derived from the WHO EML application.

  A Cochrane systematic review including 8 studies and 11,991 patients with HER2+ early breast cancer compared the efficacy of trastuzumab with the standard chemotherapy regimen. It showed the hazard risks for overall survival (OS) and disease-free survival (DFS) significantly favored the trastuzumab-containing regimens (HR= 0.66; 95% CI: 0.57-0.77; P < 0.00001 and HR= 0.60; 95% CI: 0.50 to 0.71; P < 0.00001, respectively) (*64*).

  A meta-analysis was carried out to assess the benefits of concurrent or sequential trastuzumab added to adjuvant chemotherapy for early breast cancer patients with HER2+ tumors. The analysis demonstrated benefits in disease-free survival, overall survival, loco-regional recurrence and distant recurrence (all P<0.001) from the addition of trastuzumab to adjuvant chemotherapy (*65*).

  Another meta-analysis compared the efficacy and safety of trastuzumab versus lapatinib, another anti-HER2+ agent, when added to neoadjuvant chemotherapy or versus the combination (lapatinib + trastuzumab) added to neoadjuvant chemotherapy in HER2+ breast cancer. The probability to achieve pathologic complete response (pCR) was higher for trastuzumab group (trastuzumab + chemotherapy) compared to lapatinib group (lapatinib + chemotherapy) (P < 0.001). The probability to pCR was significantly higher in the group receiving trastuzumab and lapatinib combined compared to the group with trastuzumab alone (P < 0.001) (*66*).

  Other trials of similar design have combined data from the control and the trastuzumab containing-arms in a joined analysis. Trastuzumab containing arms showed statistically significant reduction in disease free-survival event rate (P < .001) and significant reduction in death rate (P < .001) in comparison with the control arm (*67*).

  The HERA trial randomly assigned patients with HER2+ and either negative-node or positive node breast cancer that have completed locoregional therapy and at least 4 cycles of chemotherapy to 3 treatment groups (a. trastuzumab for 2 years; b. trastuzumab for one year and; c. observational group). The results of one-year treatment with trastuzumab showed less recurrence of breast cancer, contralateral breast cancer, second non breast malignant disease, or death in the trastuzumab group compared to the observation group. The unadjusted hazard ratio was 0.54 (P < 0.0001), representing an absolute benefit in terms of disease-free survival of 8.4%. Overall survival in the two groups was not significantly different (*68*).

  A 2-year follow up study of the HERA trial (*69*) showed that one year of treatment with trastuzumab after adjuvant chemotherapy has a significant overall survival benefit after a median follow-up of 2 years.

  In conclusion, most of the presented studies demonstrate that, in general, the use of trastuzumab in HER2+ early breast cancer can be associated with benefits in terms of prolonged survival (overall survival, disease-free survival) and reduction in death rate or cancer recurrence.

- Efficacy evidence for advanced metastatic HER2+ breast cancer:

  The evidence presented in the dossier is based from two main studies. The first study, Slamon trial published in 2001, showed the addition of trastuzumab to chemotherapy (cyclophosphamide plus anthracycline

or paclitaxel) compared to chemotherapy alone was associated with a longer survival (median survival of 25.1 vs. 20.3 months; P = 0.01), a lower rate of death at 1 year (22% vs. 33%, P = 0.008) and a 20% reduction in the risk of death. Moreover, the study also showed that trastuzumab addition was associated with a longer time to disease progression (median of 7.4 vs. 4.6 months; P < 0.001) and a higher rate of objective response (50% vs. 32%, P < 0.001) compared to chemotherapy alone (*70*).

The second included study, the TANDEM trial, compared the combination of trastuzumab plus anastrozole with anastrozole alone as a first-line treatment for postmenopausal women with HER2+ metastatic breast cancer. Trastuzumab plus anastrozole compared with anastrozole alone did not significantly differ in improving overall survival (median overall survival: 34.1 months vs. 28.6 months respectively (HR for death: 0.85; 95%CI not reported, P = 0.45), but the combination was superior in improving progression-free survival with 4.8 months versus 2.4 months respectively (median PFS, HR: 0.63; 95%CI: 0.47-0.84, log rank P = 0.0016) (*71*).

Both trials had evidence of moderate quality and, although the outcomes vary from one to the other, the studies establish some benefit of trastuzumab in terms of survival, progression-free survival and risk of death among the presented evidence.

To support the discussion, the Committee presented additional evidence from meta-analyses, trials and smaller studies regarding the use of trastuzumab in HER2+ advance metastatic breast cancer.

The presented meta-analysis included 8 trials (5 trials trastuzumab; 3 trials lapatinib) evaluated the efficacy of HER2+ targeted therapy (trastuzumab, lapatinib) in addition to standard treatment in metastatic breast cancer patients. Most of information provided is based on the trastuzumab trials; thus, contributing to the evaluation of this indication. The results showed that the addition HER2+ targeted agents improved overall survival, time to progression, progression-free survival and overall response rate. Patients were more likely to have a progressive disease or stable disease if they were treated with standard therapy alone (*72*).

The presented randomized multicenter trial also demonstrated first-line therapy trastuzumab plus docetaxel was significantly superior to docetaxel alone in terms of overall response rate, overall survival, time to disease progression, time to treatment failure and duration of response (*73*).

The additional evidence reviewed, while limited to a small number of studies available and of modest quality of evidence, do support the use of trastuzumab alone or in addition to other anticancer therapies to improve major clinical efficacy outcomes in patients with HER2+ advanced metastatic breast cancer. Nonetheless, the applicability of the results of proposed first-line treatment studies is limited considering that patients with HER2+ breast cancer are presently treated with other chemotherapy agents before developing metastases.

- Safety evidence for all indications:

  Trastuzumab should be avoided in pregnant women considering the potential fetal toxicity, as well as in nursing mothers. Women with childbearing potential should be advised on proper contraception therapy. The medicine has not been tested in the pediatric population; therefore, it should be avoided. Also, caution should be taken if trastuzumab is used in the elderly female population or in patients with an increased risk of cardiotoxicity and cardiac dysfunction.

- Safety evidence for early stage HER2+ breast cancer:

  As the reviewed dossier focused on the evidence supporting use in HER2+ advanced metastatic breast cancer, the Committee provided additional references, mainly derived from the WHO EML application.

A Cochrane systematic review conducted in patients with HER2+ early breast cancer, trastuzumab significantly increased the risk of congestive heart failure (P < 0.00001) and left ventricular ejection fraction decline (P = 0.0008 (*64*).

Another systematic review showed cardiac event rate was highest in the anthracycline-containing trastuzumab arms compared to the non-anthracycline arm (*74*).

Other retrospective and cohort studies also support the results of increased risk of cardiotoxicity associated with trastuzumab resulting in a reduction of LVEF and increase of symptomatic heart failure (*75, 76*).

Various other adverse events reported with trastuzumab are fever, chills, hypersensitivity, anaphylaxis, angioedema, which can be considered infusion reactions and are mainly observed with the first infusion. A risk of brain metastases has also been reported (*68*).

In conclusion, the most serious adverse events associated with the use of trastuzumab are cardiac toxicities generally expressed as a reduction in the LVEF and symptomatic heart failure (NYAC class I-IV). Nevertheless, cardiac dysfunction is mild and asymptomatic for the majority of patients. Generally, adverse events disappear once trastuzumab is stopped or discontinued. Few patients can develop more severe cardiotoxicity and may not recover fully upon treatment discontinuation. Careful cardiac monitoring is mandatory during trastuzumab treatment.

- Safety evidence for advanced metastatic HER2+ breast cancer:

As mentioned in the evidence results for safety in early stage breast cancer, the major concern with the use of trastuzumab in HER2+ advanced metastatic breast cancer is cardiotoxicity. The evidence presented in the reviewed dossier supports this safety issue for advanced metastatic HER+ breast cancer.

The Slamon 2001 trial found the addition of trastuzumab to an anthracycline in combination with cyclophosphamide was associated with higher risk of adverse events compared with chemotherapy alone. The most important adverse event was cardiac dysfunction of NYHA class III or IV; however, although the cardiotoxicity was potentially severe and, in some cases, life threatening, standard medical management generally improved the symptoms (*70*). The TANDEM trial reported a case of class II congestive heart failure among other common adverse events (fatigue, diarrhea, vomiting), higher in proportion in the trastuzumab treatment group (*71*).

To supplement the evidence provided in the reviewed dossier, the Committee provided additional evidence from smaller studies that showed a higher incidence of cardiac adverse events. The Committee reviewed a 5-year cohort study that demonstrated the incidence of cardiotoxicity did not appear to be predicted by age, comorbidity, indication, or exposure to anthracyclines and underlined that monitoring is a precondition during treatment with trastuzumab (*77*).

Other adverse events such as alopecia, infusion reactions, fatigue, diarrhea and vomiting were also present in some studies. Hematological toxicity and neurotoxicity were also reported in a short-term trial (phase II study) (*78*).

- Cost studies for all indications:

As the reviewed dossier focused on the evidence supporting use in HER2+ advanced metastatic breast cancer, the Committee provided additional references, mainly derived from the WHO EML application.

For the use of trastuzumab in HER2+ early breast cancer, the Committee provided various economic evaluations. A pharmacoeconomic review based on data from clinical trials in patients with HER2+ early

breast cancer observed that incremental costs per QALY or life-year gained with trastuzumab administered subsequent to or concurrent with chemotherapy compared with chemotherapy alone were consistently within accepted local thresholds for cost-effectiveness. Data obtained from several countries showed that the use of adjuvant trastuzumab for one year is a cost-effective treatment relative to chemotherapy alone. The results were considered generally robust (*79*).

Another 12-month cost-effectiveness study carried in an Italian and US setting demonstrated that in a long-term horizon, adjuvant trastuzumab is a cost-effective therapy for patients with HER2+, high risk, early breast cancer (*80*).

A Portuguese study evaluated the cost-effectiveness of 1-year trastuzumab treatment versus standard care in patients with HER2+ breast cancer in early stages. It concluded that the 1-year trastuzumab use as adjuvant therapy in HER2+ early breast cancer patients improves survival and can be considered a cost-effective therapy with a high degree of certainty in the Portuguese setting (*81*).

Lastly, an updated cost-utility analysis from the United Kingdom perspective concluded trastuzumab remained a cost-effective treatment strategy at a willingness-to-pay threshold of £30,000 per QALY, provided the duration of benefit was more than 3.6 years from treatment initiation and assuming the hazard ratio for disease-free survival was 0.63. Long-term cardiac toxicity needed to rise to high levels in order to affect overall life expectancy and cost-effectiveness (*82*).

These results seem to support trastuzumab use as an adjuvant therapy for at least a year is considered as a cost-effective treatment of HER2+ early breast cancer. However, as the Committee mentioned, all these studies were carried out in high-income countries. For low and middle income countries there are existing limitations such as the additional burden related to late diagnosis, reliable identification tests of HER2+ breast cancers and monitoring and control of toxicities. Thus, the available evidence cannot be interpreted in the same manner for low and middle income countries.

The Committee discussed the experiences from Costa Rica, which has incorporated trastuzumab in the national Social Security system since 2006. An evaluation carried with 93 patients showed that trastuzumab, used as an adjuvant for HER2+ breast cancer in 2006-2007, resulted in a survival of 6.5 years with an NNT of 1.3 underlining an investment of US$32,971. However, no other economic analyses from low and middle income countries were discussed. The Committee agreed that further cost-effectiveness data specific to the Region would help orient decisions.

Specific to HER2+ advanced metastatic breast cancer, the cost studies presented in the dossier were not able to conclude trastuzumab is a cost-effective treatment. Despite comparative efficacy being demonstrated in a set of randomized controlled trials, the systematic review presented in the dossier showed different results regarding the cost-effectiveness of trastuzumab and could not agree on a final conclusion. The economic evaluations used different thresholds to determine whether treatment with trastuzumab was cost-effective and many of the potential drivers were not identified by the published systematic reviews of economic evaluations, and perhaps more remain unidentified because of inconsistent and limited reporting (*83*).

The economic evaluations with the most feasible results were those presented in the NICE technology appraisals. The NICE technology appraisal guidance concluded that trastuzumab combination therapy was likely to be lower than £37,500 per QALY gained. On the other hand, the NICE technology appraisal guidance 257 concluded that the most plausible incremental cost-effectiveness ratio (ICER) for trastuzumab plus an aromatase inhibitor would be at least £51,000 per QALY gained (*84,85*).

Overall, because of different conclusions regarding the cost-effectiveness of trastuzumab, treatment of metastatic breast cancer with trastuzumab has not been consistently accepted as cost-effective.

- Additional comments discussed at meeting:
  - NA
- Recommendation:

  In the light of the presented evidence, the Committee agreed there is sufficient evidence to recommend the inclusion of trastuzumab for the treatment of HER2+ early breast cancer in the Strategic Fund Medicine List; however, there is not sufficient evidence to include trastuzumab for advanced metastatic HER2+ breast cancer. The Committee recommends inclusion for two presentations of trastuzumab: 150mg and 440mg powder for injection.

  The use of trastuzumab in HER2+ early breast cancer can be associated with prolonged survival and reduction in death rate or cancer recurrence. The efficacy of trastuzumab is well supported by various studies carried in early breast cancer patients, where trastuzumab proved to be effective to reduce morbidity and mortality.

  The reasonable safety profile, as well as the current available evidence with regards to efficacy and cost-effectiveness, justifies the inclusion of trastuzumab in PAHO Strategic Fund Medicine List for the treatment of HER2+ early breast cancer. Additionally, the profile of patients who are selected to receive the medicine is more favorable to better response and can be considered as cost-effective. Various international guidelines also support the use of trastuzumab as an adjuvant or neoadjuvant to chemotherapy regimens in HER2+ early breast cancer.

  Considering the high cost of this medicine and limitations encountered due to the presence of a sole source supplier, the PAHO Strategic Fund can lower prices through consolidating Regional demand and leveraging economies of scale. Nonetheless, countries planning procurement of trastuzumab will need to ensure availability of the necessary infrastructure for proper diagnosis, treatment and monitoring of the therapy. Trained medical staff and adequate storage conditions are required. The Committee agreed that the narrow margin of benefit emphasizes the need for appropriate patient selection as well as the importance of a health care system that has the diagnostic, treatment and monitoring modalities required to manage the use of trastuzumab.

  Specific to advanced metastatic HER2+ breast cancer, the Committee agreed that although various efficacy studies appear to improve major clinical efficacy outcomes, the small number of studies and the modest quality of evidence is not robust enough to demonstrate clearly the effectiveness and safety of trastuzumab in HER2+ advanced metastatic breast cancer. Moreover, cost studies have reached no consensus regarding the cost-effectiveness of trastuzumab. Hence, treatment with this medicine has not been consistently accepted as cost-effective.

3. Transplant and Immunosuppression Medicines

In 2011, the Global Observatory on Donation and Transplantation (GODT) stated 10,922 kidney transplants, 2,377 liver transplant and 425 heart transplants were performed in 18 countries from Latin America. The increasing trend of organ donation and transplantation in the Region of the Americas demonstrates the necessity for optimal effective and safe pharmacotherapy to prevent graft rejection and ensure patient's survival (*86-88*).

As newer immunosuppressant medicines have become available, various countries from the Region have expressed interest in procuring immunosuppressant medicines to prevent graft rejection through the PAHO Strategic Fund. Additionally, the Red/Consejo Iberoamericano de Donación y Trasplantes (RCIDT) has re-

quested PAHO to assist in increasing access to immunosuppressants in the Americas. To respond to the needs of Member States, the Regional Advisor for Blood Transfusion and Organ Transplant from the PAHO Medicines and Health Technologies Unit (HSS/MT) submitted and supported applications of mycophenolate mofetil, sirolimus and tacrolimus for inclusion in the PAHO Strategic Fund Medicine List.

Below is a summary of the Expert Committee's review of mycophenolate mofetil, sirolimus and tacrolimus and their corresponding recommendations.

3.1 Mycophenolate Mofetil

The efficacy, safety and cost of mycophenolate mofetil were reviewed compared to azathioprine, the alternative treatment currently available in the PAHO Strategic Fund Medicine List and the WHO EML, for three clinical indications (kidney, liver and heart transplants).

The experts who reviewed this application were Dr. Facundo Garcia Bournissen and Dr. Carlos Alberto Cuello-García.

- Efficacy evidence for kidney transplants:

  A systematic review of 19 trials with kidney transplant patients has showed that there is moderate quality evidence demonstrating mycophenolate mofetil (MMF) reduces the risk of rejection and acute graft loss compared to azathioprine (AZA). The results showed a 24% reduction of graft loss with MMF compared with AZA (HR 0.76 95%CI [0.59-0.98]) and a 38% reduction in acute rejection (RR 0.62 95% CI [0.55-0.70]). No significant differences were observed in other outcomes such as survival, graft function or overall risk of adverse events in kidney transplantation studies (*89*).

- Efficacy evidence for liver transplants:

  Concerning liver transplantation, the available evidence is of lower quality than the evidence supporting kidney transplantation. Based on the results of a systematic review including 3 RCTs, MMF reduced the risk of acute rejection compared to AZA (38.5% versus 47.7%, p = 0.02 based on largest trial, N = 565). However, no significant differences were observed in patient and graft survival or rate of adverse events (infection, gastrointestinal symptoms, leucopenia) suggesting that MMF is just as effective and safe as AZA regarding those outcomes. One study (N = 63) included in the systematic review showed thrombocytopenia was significantly less frequent for MMF compared to AZA (19.4% MMF versus 46.9% AZA; $p < 0.05$), but the trial with the largest sample did not demonstrate any statistical significant difference in regards to thrombocytopenia. For liver transplants, the lack of large randomized clinical trials and the poor quality of the evidence limits the applicability of the findings and of the clinical benefits of MMF over AZA (*90*).

- Efficacy evidence for heart transplants:

  The data supporting the use of MMF over AZA in heart transplant is limited and of very low quality. No systematic review has been identified and the presented evidence is based on a relatively large multicenter study (650 patients). The available evidence suggests that MMF, compared to AZA, reduces the risk of death (deaths 34/289 vs. 53/289), reduces the need for a subsequent heart transplant and increases time lapse for re-transplantation. Also, MMF can allow for lower doses of cyclosporine (CYP) to be used (91). The use of MMF for CYP dose reduction is also supported and recommended by clinical practice guidelines from the International Society of Heart and Lung Transplantation Guidelines (*92*).

- Safety evidence for all indications:

Concerning the safety of MMF, the available evidence does not suggest significantly larger risk of adverse events compared to AZA. Some studies noticed an increase in gastrointestinal symptoms; however, more serious drug reactions such as severe infections, malignancies or hematological abnormalities seem to be comparable for both medicines (*89,90*).

Nonetheless, the results of the clinical trial in heart transplant (N = 650) showed the risk of tissue invasion by herpes simplex (HS) and cytomegalovirus (CMV) was greater for MMF than for AZA (HS: MMF 66/289 (22.85%), AZA 46/289 (15.9%) $p < 0.05$; CMV (MMF 38/289 (13.1%); AZA 25/289 (8.7%), $p < 0.05$) (*91*). Another important safety aspect to be considered is the known teratogenicity of MMF compared to AZA and the Committee agreed MMF should be avoided during pregnancy.

- Cost:

  In terms of comparative costs, no cost-analysis economic evaluations were available for liver and heart transplants comparing MMF to AZA. Some studies conducted with kidney transplant patients suggested cost increases when MMF was used instead of AZA in the short term (6months-1 year). Two other studies have estimated both the cost and the effectiveness of MMF to be superior to AZA after 10 years in kidney transplant patients (*93*). To determine the cost benefit of MMF over AZA, more robust and relevant data is needed regarding economic analyses of MMF in kidney transplant but most of all in heart and liver transplant.

- Additional comments discussed at meeting:

  - NA

- Recommendation:

  The Committee recommended the inclusion of MMF in the Strategic Fund Medicine List for prophylaxis of organ rejection in adult patients receiving allogeneic renal transplants; however, there was not enough evidence for inclusion in adult patients receiving allogeneic cardiac or hepatic transplants. The Committee agreed to include both presentations of MMF, 250mg capsules and 500mg tablets.

  MMF is regarded as a standard treatment in many transplant guidelines and based on the presented evidence it is considered as good as or better than AZA in terms of efficacy and safety only for renal transplants. The Committee concluded that the presented evidence for heart and liver transplants is not as robust as the evidence available for kidney transplants.

  The cost of MMF is higher than AZA and the lack of economic evaluations does not allow for a cost-effectiveness comparison; however, the Committee agreed that economies of scale can be obtained if MMF is included in the Strategic Fund Medicine List.

  In conclusion, the Committee agreed the available evidence supports increasing access of MMF for adult patients receiving allogeneic renal transplants and recommends PAHO assist Member States consolidate demand of MFF to lower the cost through leveraging economies of scale.

3.2 Sirolimus

The efficacy, safety and cost of sirolimus were reviewed compared to calcineurin inhibitors and antiproliferative metabolites for two indications (kidney and heart transplant). Comparison was made with products currently published in the PAHO Strategic Fund Medicine List and the WHO EML (CYP and AZA) and two applicants reviewed by this Committee (MMF and tacrolimus).

The experts who reviewed this application were Dr. Lisa Bero, Dr. Perla M. de Buschiazzo and Dr. Carlos Alberto Cuello-García.

- Efficacy evidence for kidney transplants:

A Cochrane systematic review assessed the benefits and harms of sirolimus (SRL) and presented pooled results of studies in which the comparison interventions were CYP or tacrolimus (TAC) in kidney transplant patients. The review demonstrated high quality of evidence for SRL compared to calcineurin inhibitors (CNI), TAC and CYP and showed similar rates of mortality (RR 0.98; 95%, CI 0.39 to 2.48), total graft loss (RR 1.03; 95%, CI 0.50 to 2.14) or acute rejection rate (RR 1.03; 95%, CI: 0.74 to 1.44). The results were limited to a 2-years period (*94*).

The same Cochrane Systematic review also assessed the benefits and harms of SRL compared to MMF or AZA, two antimetabolites. High quality evidence demonstrated similar rates of mortality (RR 1.10; 95%, CI 0.67 to 1.81), total graft loss (RR 1.08; 95%, CI 0.81 to 1.44) or acute rejection (RR 0.84; 95%, CI: 0.65 to 1.10).

- Efficacy evidence for heart transplants:

For heart transplant treatment, no systematic reviews were identified assessing the effectiveness of SRL in comparison with calcineurin inhibitors (CYP and TAC) or antimetabolites (AZA and MMF). The results presented are based on 3 main clinical trials. One trial compared directly SRL versus AZA and the remaining trials compared different combinations for SRL (SRL and TAC or SRL and MMF). Very low quality of evidence showed SRL (3mg and 5mg) reduced the episodes of acute rejection compared to AZA. Also, comparisons of the combinations of SRL and MMF, TAC and MMF or TAC and SRL do not show a statistical difference in survival. No other relevant clinical outcomes were measured in the trials (*95-97*).

All presented evidence was considered of very low quality. The high risk of bias present, the small sample sizes, the lack of information on patients' characteristics as well as the financial support provided by pharmaceutical companies demonstrate the methodological weakness of the studies and conflict of interests. The measured interventions and outcomes were inconsistent through the trials as they were defined and measured with varying methodologies within the studies.

- Safety evidence for kidney transplants:

The results presented in the Cochrane systematic review showed no statistically significant differences in the risk malignancy, new-onset diabetes requiring insulin and hypercholesterolemia when SRL was compared to CNI (CYP or TAC) in kidney transplanted patients. On the other hand, SRL showed a statistically significant decrease in creatinine and an increase in glomerular filtration rate in comparison with CNI. Regarding other adverse events, SRL had an increased risk of lymphocele and bone marrow suppression (anemia, leucopenia, thrombocytopenia) and was more likely to require drug treatment for lipid disturbance compared to CNI (*94*).

Compared to antiproliferative metabolites (MMF and AZA), the Cochrane systematic review data showed SRL increases serum creatinine, increases the risk of hypercholesterolemia but does not show difference in the risk of malignancy or new-onset diabetes requiring insulin (*94*).

- Safety evidence for heart transplants:

The safety results trials in heart transplanted patients are supported by 3 clinical trials and considered of very low quality of evidence. The measured interventions and outcomes were inconsistent through the trials as they were defined and measured in different ways within the studies. In terms of adverse events, some of the available data showed that SRL increase the risk of pneumonia compared to AZA. Also, a trial

demonstrated the combination of SRL /TAC increased median serum creatinine compared to TAC/MMF or CYP /MMF in heart transplant patients (*95-97*).

- Cost:

  Limited amount of economic evaluations were found in order to support the cost-effectiveness of using SRL instead of calcineurin inhibitors or antiproliferative metabolites. An economic evaluation synthesized a study using the Morkov model to estimate the cost-effectiveness of four triple immunosuppression regimens available for renal transplant patients. The main measures of benefit were the cost per life-year gained and the cost per year with a functioning graft gained. The results showed that SRL dominated everolimus and TAC over a period of two years, as everolimus and TAC were more costly and less effective. After 10 years, SRL would dominate CYP and everolimus (*98*).

  No economic analyses comparing SRL to antiproliferative metabolites (MMF and AZA) or for heart transplant patients were available.

- Additional comments discussed at meeting:

  - NA

- Recommendation:

  In the light of the presented evidence, the Committee recommended rejecting inclusion of SRL in the Strategic Fund Medicine List for the prophylaxis of organ rejection in adult patients receiving allogeneic renal and cardiac transplants.

  For kidney transplantation, the Committee agreed that the high quality evidence available shows no difference in efficacy (similar rates of mortality, total graft loss, acute rejection) compared to calcineurin inhibitors (TAC and CYP) or antiproliferative metabolites (MMF and AZA).

  For heart transplantation, the data available is insufficient or of poor quality and cannot support the use of SRL in heart transplant patients.

  In conclusion, SRL does not provide sufficient benefit in comparison to alternative treatments already available in the Strategic Fund Medicine List.

3.3 Tacrolimus

The efficacy, safety and cost of tacrolimus were reviewed compared to cyclosporine, the alternative treatment currently available in the PAHO Strategic Fund Medicine List and the WHO EML, for four clinical indications (kidney, liver, heart and bone marrow and stem cell transplants).

The experts reviewing this application were Dr. Lisa Bero, Dr. Edgard J. Narváez Delgado and Dr. Perla M. de Buschiazzo.

- Efficacy evidence for kidney transplants:

  High quality evidence provided by a Cochrane systematic review states TAC compared to CYP significantly reduced graft loss (7 RCT 1552 patients; RR 0.56, 95% CI 0.36 to 0.86) and this effect was persistent up to three years (7 RCT, 1513 patients; RR 0.71, 95% CI 0.52 to 0.96) (39%). At one year, TAC patients suffered less acute rejections (14 RC, 2751 patients; (RR 0.69, 95% CI 0.60 to 0.79) and less steroid-resistant rejection (9 RCT, 1770 patients; RR 0.49, 95% CI 0.37 to 0.64). In order to apply the review results in clinical practice, Cochrane provides absolute risk per 100 treated recipients. The analysis

concluded that treating 100 low risk patients with TAC instead of CYP would avoid 6 acute rejections. This absolute risk per 100 would rise to 17 if considering high risk populations (sensitized recipients of subsequent grafts). Meta-regression results showed that when TAC is used, targeting through levels will minimize graft loss (*99*).

- Efficacy evidence for liver transplants:

  High quality evidence provided by a Cochrane systematic review stated that in liver transplanted patients, TAC compared to CYP resulted in a 15% reduction of mortality at one year in the TAC group (16 RCT, 3813 patients; RR 0.85, 95% CI 0.73 to 0.99). Graft survival was reported in 15 trials, showing a 22% relative reduction favoring TAC over CYP (16 RCT, 3,813 patients; RR 0.78, 95% CI 0.68 to 0.89) and reduced acute rejection and steroid resistant rejection by 18% and 43% respectively (RR 0.82, 95% CI 0.77 to 0.88; RR 0.57, 95% CI 0.46 to 0.71) in the TAC group (*100*).

- Efficacy evidence for heart transplants:

  Moderate quality evidence provided by a systematic review with 14 meta-analyses showed no difference between TAC and CYP in mortality (10 RCT, 952 patients; RR 0.78; 95%CI 0.54 to1.13); however, a difference was noted when TAC was compared to microemulsion CYP (7 RCT, 760 patients; RR 0.64; 95%CI 0.42 to 0.96; p= 0.17). The significant difference in mortality between TAC and microemulsion CYP disappeared when the studies including pediatric patients were excluded from the analysis (RR 0.66; 95% CI 0.40 to 1.09). No significant difference in mortality was observed between TAC and oil-based CYP (3 RCT, 192 patients; RR 1.79; 95% CI 0.77 to 4.15, p = 0.17) (*101*).

  Furthermore, the review did not show a difference in the number of patients with 3A or higher rejection when comparing TAC and CYP (5 RCT, 700 patients, RR 0.86; 95% CI 0.62 to 1.20), but found a significant reduction when TAC was compared to microemulsion CYP (4 RCT, 615 patients; RR 0.71; 95% CI 0.56 to 0.90, p = 0.004). No differences were found in rejection causing haemodynamic instability when compared to microemulsion CYP (5 RCT; RR 0.96; 95% CI 0.34 to 1.38) (*101*).

  The applicability of these results should be considered according to the poor methodological quality of the trials, the small number of events in some outcomes and the lack of data to make appropriate judgments about the quality of evidence. Another point to be considered is that one of the formulations compared (oil-based) is not the preparation currently marketed.

- Efficacy evidence for bone marrow and stem cell transplants:

  No systematic reviews were found when comparing TAC to CYP in the treatment of bone marrow and stem cell transplants. The evidence available in the reviewed dossier is based on 3 randomized controlled trials and is considered of low quality. The trials were heterogeneous in terms of patients and combinations of the medicines utilized. The applicability of the results is limited due to the number of trials, participants and events in the analyses. The evidence of all 3 trials was pooled for final conclusions regarding various outcomes. The results showed significant reduction in the incidence of grade II-IV acute graft versus host disease (GVHD) of TAC group compared to CYP. No difference was observed in grade III-IV acute GVHD, chronic GVHD, relapse rates and engraftment between the two treatments. Regarding survival, results are inconsistent through the 3 studies; hence, no firm conclusion can be drawn regarding the risk of mortality (*102-104*).

- Safety evidence for kidney transplants:

  In terms of safety, high quality evidence shows that in kidney transplant patients, the use of TAC compared to CYP increases the risk of post-transplant diabetes (RR 1.86, 1.11 to 3.09) as well as neurological and

gastrointestinal adverse events. The meta-regression of the Cochrane review calculated that every 100 patients treated with TAC would cause an extra 5 additional cases of diabetes mellitus, as opposed to CYP. Conversely, CYP was associated with more constipation and cosmetic side effects. No differences were found in the rate of malignancies (*99*).

- Safety evidence for liver transplants:

  High quality evidence from the assessed Cochrane review showed that more patients discontinued CYP than TAC (RR 0.65, 95% CI 0.57 to 0.74). Patients in the TAC group had a rate of new-onset diabetes increased by 27% compared to CYP (RR 1.27, 95% CI 1.12 to 1.44). The Cochrane review calculated that every 100 patients treated with TAC instead of CYP would cause 4 cases of new-onset diabetes post-transplantation. No differences were seen in the rates of chronic renal failure requiring dialysis or in the number of lymphoproliferative disorder after liver transplantation (*100*).

- Safety evidence for heart transplants:

  Low quality evidence suggests that TAC reduces the risk of hypertension, reduces the need of medication to treat hyperlipidaemia, reduces the cholesterol level, but increases the risk of post-transplant diabetes when compared to CYP. Also, TAC has a lower risk of gingival hyperplasia and hirsutism compared to CYP. No significant differences were observed in infection, renal failure, malignancies, neurotoxicity and chronic allograft vasculopathy (*101*).

- Safety evidence for bone marrow and stem cell transplants:

  Low quality evidence pooled from 3 clinical trials, suggests that TAC increases the incidence of renal adverse effects compared to CYP in adult bone marrow and stem cell transplant. The nephrotoxicity of TAC may be related to their blood levels, further studies are needed to define the drug levels to minimize toxicity while preserving a high level of immunosuppressive effect of TAC (*102-104*).

- Cost:

  The economic studies included in the review of literature varied in terms of quality and evaluation frameworks. The results presented were consistent to conclude that TAS (tacrolimus, azathioprine and a corticosteroid) is a more cost-effective option compared to CAS (cyclosporine, azathioprine, and a corticosteroid) in kidney transplanted patients. Six of the twelve studies concluded that the healthcare costs associated with TAS were lower than those for CAS. However, the economic evaluations contained a number of methodological limitations, undermining the confidence that can be attached to their results (*105*).

  With respect to liver transplantation, an assessed economic evaluation published in 2001 found TAC, used as a primary immunosuppressant in liver transplantation, to be superior to CYP based on an estimated cost of transplantation at 6 months post-transplantation. The estimated total cost per day of TAC group was US$13.69 per day and US$27.17 per day for the CYP group. Sensitivity analyses were not conducted; thus, the external validity of the analysis is relatively low (*106*).

  No economic studies were found in heart transplant and bone marrow and stem cell transplant.

- Additional comments discussed at meeting:

  - The Committee highlighted the importance of the formulation of TAC as there are observed differences in the benefit risk ratio between the immediate and prolonged-release formulation.

- Recommendation:

The Committee recommended the inclusion of TAC 0.5, 1 and 5 mg capsules (immediate release) in the Strategic Fund Medicine List for prophylaxis of organ rejection in adult patients receiving allogeneic renal and hepatic transplants; however, there was not enough evidence for inclusion in adult patients receiving allogeneic cardiac or bone marrow and stem cell transplants.

High quality evidence showed TAC improves graft survival, reduces the risk of acute rejection and steroid–resistant rejection after kidney transplantation compared to CYP although the risk for diabetes and other adverse events may potential increase. In liver transplantation, high quality evidence also supported the efficacy and acceptable safety profile of TAC compared to CYP while showing it reduced risk of mortality, improved graft survival and reduced risk of acute rejection and steroid resistant rejection. However, it also increased the risk of post-transplant diabetes. Nonetheless, the benefit risk ratio for these two indications supports the inclusion of TAC as an alternative treatment to CYP.

Conversely, the evidence for heart transplant and bone marrow and stem cell transplant is less rigorous and of lower quality. The poor quality of the reviewed studies as well as the risk of bias did not lead to significant differences in clinically relevant outcomes when TAC was compared to CYP. This further emphasizes the need for good quality randomized controlled trials focused on patient outcomes to determine a robust benefit risk ratio of TAC compared to CYP.

The inclusion of TAC will increase access to an effective immunosuppressant with an acceptable safety profile for kidney and liver transplant treatment and inclusion in the Strategic Fund Medicine List should enable cost reductions for Member States.

Summary of Recommendations

The PAHO Director will review the Committee's recommendations and make a final decision for inclusion or otherwise into the PAHO Strategic Fund Medicine List. Upon receiving the Director's final judgment, the Secretariat will publish an updated version of the PAHO Strategic Fund Medicine List. The list will be available at www.paho.org/strategicfund.

1. Inclusion

The Committee recommended including six applications (chlorthalidone, clopidogrel, losartan, mycophenolate mofetil, tacrolimus and trastuzumab) in the PAHO Strategic Fund Medicine List, which should be published in the following manner:

International Nonproprietary Name (INN) or Generic Name	Strength	Presentation	Indication(s)	Ref
CARDIOVASCULAR MEDICINES				
Antihypertensive medicines				
Chlorthalidone	12.5 & 25 mg	Tablet	Hypertension in adults	
Losartan	25, 50 & 100 mg	Tablets	Hypertension in adults	1
Antithrombotic medicines				
Clopidogrel	75 mg	Tablet	Prevention of atherothrombotic events in adults with non-ST segment elevation acute coronary syndrome	
ANTINEOPLASTIC, IMMUNOSUPPRESSIVES AND MEDICINES USED IN PALLIATIVE CARE				
Cytotoxic medicines				
Trastuzumab	150 & 440 mg	Powder for injection	HER2+ early breast cancer	
Immunosuppressive Agents				
Mycophenolate Mofetil	250 mg	Capsules	Prophylaxis of organ rejection in adult patients receiving allogeneic renal transplants	
	500 mg	Tablets		
Tacrolimus	0.5, 1, 5 mg	Capsules (immediate release)	Prophylaxis of organ rejection in adult patients receiving allogeneic renal or hepatic transplants	

1: Losartan can be used as an alternative for treatment of adults with hypertension for those patients in whom ACEi are indicated but not tolerated, specifically due to the presence of adverse events (mainly cough); including the sub-population of hypertensive patients associated with type II diabetes with proteinuria.

2. Rejected Applications

The Committee recommended rejecting inclusion of two applications (lisinopril and sirolimus) in the PAHO Strategic Fund Medicine List:

- Lisinopril:
  - For hypertension and heart failure treatment the provided evidence did not support the superiority of lisinopril' s efficacy and safety compared to other ACEi, specifically for the compared medicine (enalapril), and
  - In conclusion, the Committee noted enalapril, which is already in the Strategic Fund Medicine List, and lisinopril share a similar benefit risk ratio and lisinopril has a higher cost. Hence, the inclusion of lisinopril is not justified.
- Sirolimus:
  - For kidney transplantation the evidence available shows no difference in efficacy compared to calcineurin inhibitors or antiproliferative metabolites and for heart transplantation, the data available is insufficient or of poor quality and cannot support the use of sirolimus, and
  - In conclusion, sirolimus does not provide sufficient benefit in comparison to alternative treatments already available in the Strategic Fund Medicine List.

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Annex 1

Review of the Available Evidence of Chlorthalidone 50mg Tablet for Potential Inclusion in the Pan American Health Organization Strategic Fund Medicine List

Annex 1: Table of Contents

1. Introduction to the PAHO Strategic Fund

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (Strategic Fund) was created by the Director of the Pan American Health Organization (PAHO) at the request of Member States of the Organization, in September 1998 during the 35th session of the Pan American Sanitary Conference.

The Strategic Fund is a regional mechanism which aims to strengthen the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe and effective supplies at affordable prices obtained by leveraging the advantages of economies of scale.

To accomplish this objective the Strategic Fund publishes a list of medicines available for procurement in name of the Organization's Member States. The list utilizes as a foundation the World Health Organization (WHO) Essential Medicines List (EML); however, recently there has been a significant increase in Member State requests to procure products not included in the WHO EML.

In order to meet the needs of PAHO Member States the PAHO Director has created an external Expert Committee to review requests for inclusion of medicines not included in the WHO EML. This Expert Committee will allow PAHO to implement a decision making mechanism in agreement with concepts of quality, efficacy, safety and when available, information related to the value they provide in relation to their cost.

The committee will work exclusively on requests to update the SF medicine list, which will enable PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this EC should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

2. Public Health Relevance (*1-3*)

2.1 NCDs in the Region of the Americas

Over the last decades, noncommunicable diseases (NCDs) have become the leading cause of morbidity and mortality across the globe while imposing a growing threat to international development goals and economic growth as well as contributing to dramatic rises in health care expenditures.

The main NCDs principally include cardiovascular disease, cancer, diabetes and respiratory diseases and are accompanied by various common risk factors rising at a rapid pace. In the Americas region, NCDs are responsible for 3 out of every 4 deaths with cardiovascular diseases and cancer as the leading causes responsible respectively for 1.9 million and 1.2 million deaths each year. More than one third of these deaths are premature and occur in people under the age of 70 years old therefore leading to serious repercussions on social and economic development.

Noncommunicable diseases not only slow down development but also place a heavy financial burden on patients, healthcare and governments. The costs to overall health systems are expect to rise as governments are expected to increase funding to prevent and treat these diseases. Confronting the rising costs constitutes a real challenge in low and middle income countries of the Americas where economic growth is often compromised and healthcare systems have to manage access and equity issues. Patients are facing similar issues, as in many countries healthcare costs are paid out-of-pocket and the impact of NCDs on household budgets and healthcare expenditures can often lead to catastrophic spending and impoverishment.

In some countries of the region, out-of-pocket expenditures account for 78% of spending on medicines. Cardiovascular diseases constitute an important family expenditure on healthcare and can become an enormous economic and social burden in low-and-middle income countries. For example, patients suffering from more than two chronic diseases and taking more than two medicines for these conditions account for 10% of all patients in some countries. Health expenditures for this population can reach 50% of the overall health expenditure. Hence, in Latin America, out-of-pocket expenses related to NCDs and health expenditures accounting for chronic diseases represent a critical health care and financial issue.

In response to the NCD situation in the Americas, the 28th Pan American Sanitary Conference in September 2012, adopted the Regional Strategy for the Prevention and Control of Noncommunicable Diseases (Resolution CSP28.R13 aims to:

> "reorient and strengthen health systems to improve coverage, access to and quality of care provided to the people with NCDs or their risk factors, based on primary health care"

This process is linked with the WHO voluntary global NCD targets for 2025, which aims to achieve the following:

- 25% relative reduction of premature mortality due to noncommunicable diseases
- 80% coverage of essential NCD medicines and technologies
- 50% coverage of drug therapy and counseling.

As a critical component of PAHO's response to these issues, the Strategic Fund is increasing support and assistance to Member States by amplifying the list of NCD medicines for countries to procure. Thus, increasing access to quality drugs and helping ease the increasing financial burden, specifically for new or high cost medicines.

The Strategic Fund has initiated a process to review the available evidence regarding the efficacy, safety and cost-effectiveness of NCD medicines, particularly for cardiovascular diseases and cancer. The following document presents the status of the medicine, basic pharmacological information, the evidence comparing the requested medicine and its alternative for the specified indications and other relevant information.

2.2 Cardiovascular Health Situation in the Americas

Cardiovascular diseases (CVD) are the main leading cause of death globally and accounts for 30% of deaths annually worldwide. In 2007, cardiovascular diseases caused 1.5 million deaths in the Region of the Americas where approximately 40% occur prematurely at an early stage of productive life. Among risk factors such as obesity, hypercholesterolemia and smoking, hypertension is the greatest risk factor for CVD and accounts for 62% of strokes and 49% of ischemic heart disease. Recent data states 18% of the adult population in Latin America suffers from hypertension. Therefore, the control of hypertension becomes the central focus in reducing cardiovascular disease risk.

Early detection and effective pharmacological treatments are crucial in order to reduce hypertension incidence and prevalence among the Region's population, but also to prevent further consequences such as stroke, acute coronary syndrome, congestive heart failure, and others. In low and middle income countries such as in the Americas, the best evidence-based approach for CVDs is a multidrug combination (aspirin, two antihypertensive medicine, and statins) for patients at high risk of cardiovascular disease or who already had a past cardiovascular event.

Considering these diseases and risk factors are more prevalent among poor populations and affect to a greater extend the vulnerable and socially disadvantaged, PAHO aims to increase access to quality medicines to prevent and treat cardiovascular diseases and decrease the financial burden they can represent.

3. Entity Supporting the Application and Requested Indications

3.1 Entity Supporting Application

The PAHO Noncommunicable Diseases and Disabilities Unit (NMH/ND) is requesting and supporting this application.

3.2 Requested Indications

Chlorthalidone, an antihypertensive thiazide diuretic has been requested for the treatment of hypertension and heart failure in an adult population.

4. Medicine Characteristics and Pharmacological Information (*4-8*)

4.1 General Information

1) Medicine name (INN)	Chlorthalidone
2) ATC (anatomical therapeutic chemical- WHO Drug classification system)	C03BA04
3) Reference trade name: (1. Innovator & 2. Generic - when available some examples provided)	1. Innovator: Hygroton 50mg (Sanofi Aventis - US FDA discontinued) 2. Generic: Chlorthalidone 50mg (Mylan) and Chlorthalidone 50mg (PLIVA)
4) Therapeutic class (according to classification in the WHO EML)	Antihypertensive- Diuretics- Thiazides

4.2 Mechanism of Action

Chlorthalidone acts as a diuretic by enhancing excretion of sodium, chloride and water on the cortical diluting segment of the ascending limb of Henle's loop of the nephron by interfering with the transport of ions across the renal tubular epithelium. Thiazides can also affect the excretion of other electrolytes but to a lesser extend (potassium, bicarbonate, magnesium, calcium, phosphate, etc.)

4.3 Pharmacokinetic/Pharmacodynamics Considerations

- *Absorption*: In gastrointestinal tract, little information is available on the extend of the absorption of the drug
- *Distribution:* Plasma protein binding (75-90%), long half-life $T_{1/2}$(40-60hours), crosses placenta, found in breast milk

- *Metabolism:* None, CYP450: none
- *Excretion:* Unchanged in urine (50-75%); bile

4.4 Dosage, Preparation and Administration

- *Dosage and Administration*:
  - Chlorthalidone 50mg tablets are administered orally. Take in the morning, with food. The dosage of chlorthalidone should be individualized according to the indication and to the patient's response. Moreover, if the patient is already using other hypotensive medicine, the dosage of this hypotensive medication should be reduced in order to decrease the risk of severe hypotension.
- *Hypertension:*
  - The initial dosage is 12.5-25mg once daily; Titrate: the dose may be increased to 50mg once daily until therapeutic response (blood pressure control). If additional control is required, the dose can be increased to 100mg once daily or a second anti-hypertensive can be added to the therapy; Max: 100mg once daily
- *Heart failure*:
  - Treatment of edema: the initial dosage is 50-100mg once daily or 100mg once (every other day); Titrate: the dose may be increased to 150-200mg once daily or once every other day; Max: 200mg once daily

4.5 Contraindications

- Anuria
- Hypersensitivity to thiazides or to other sulfonamide-derived drugs (not absolute)
- Pregnancy (category B) and lactation (safety unknown)

4.6 Warnings/Precautions

- *Caution with severe renal disease*
  - Can precipitate azotemia and decrease GFR, cumulative effects with progression of renal disease. If renal disease progresses consider dose reduction or discontinuing thiazide therapy
- *Caution with hepatic impairment*
  - May precipitate hepatic coma resulting in alterations in electrolyte balance
- *Caution with parathyroid disease*
  - Pathologic changes in the parathyroid gland in patients with hypercalcemia and hypophosphatemia; occurs infrequently
- *Caution with diabetes mellitus*
  - Thiazides can produce hyperglycemia and glycosuria in diabetics and diabetes can be precipitated in prediabetic patients
- *Caution with the combination of other anti-hypertensive medications*
  - Risk of severe hypotension
- *Caution with gout*

- Hyperuricemia may occur or gout precipitated in patients with history of gout, familial predisposition or chronic renal failure

- *Electrolyte disturbances*
  - Dilutional hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia may be aggravated and sometimes lead to serious adverse effects or toxicities (cardiac arrhythmias in cases of hypokalemia)

4.7 Side Effects

Common	Serious and rare:
• Orthostatic hypotension • Dizziness • Headache • Muscle weakness • Gastric irritation • Nausea/vomiting • Constipation • Impotence • Rash • Urticaria • Electrolyte imbalance	• Arrhythmias, Agranulocytosis • Leukopenia • Thrombocytopenia pancreatitis • Pulmonary edema

4.8 Main Interactions

Drug	Interaction
Drugs affected by or causing potassium depletion	Digitalis glycosides, corticosteroids, corticotropin and amphotericin B can lead to cardiac toxicities because of potassium depletion
Lithium	Chlorthalidone can decrease lithium renal clearance thus increasing risk of lithium toxicity
Antidiabetic agents (insulin or oral agents)	The hyperglycemic effect of chlorthalidone can result in the temporary loss of diabetic control and can require adjustments of antidiabetic agents
Hypotensive agents	Example of potent hypotensive agents such as guanethidine sulfate, methyldopa or ganglionic blocking agents that could lead to severe postural hypotension
Probenecid	Probenecid can alter electrolytes and uric acid levels
Non steroid anti-inflammatory agents (NSAIDs)	NSAIDs can increase the risk of renal failure and interfere with the diuretic and antihypertensive response
Medicines with phototoxic potential	Hydroquinone/retinoid combos, aminolevulinic acid topical can increase risk of phototoxicity
Alcohol, barbiturates and opiates	Contribute to increase the postural hypotensive effects of chlorthalidone

4.9 Other

- *Photosensitive*
- *Monitoring parameters*

- CR at baseline, electrolytes at baseline then periodically

- *Diet specificities*
  - Low-sodium diet and increase amounts of potassium-rich food (bananas, orange juice, prunes, raisins, etc.) if applicable.
- Laboratory test interferences
  - Test of parathyroid function (can alter calcium levels); tyramine and phentolamine tests because it can cause false-negative; probably the histamine test for pheochromocytoma.
- Storage
  - 20-25 °C (68-77°F)

5. Alternatives to Chlorthalidone Available in the Strategic Fund

The Strategic Fund list already includes an alternative diuretic of the same class of thiazides, hydrochlorothiazide. Hydrochlorothiazide is also listed on WHO Essential Medicine List.

The following document provides the supporting evidence regarding the comparison of Chlorthalidone and Hydrochlorothiazide in the treatment of hypertension and heart failure. This document does not represent a therapeutic guideline for treatment of these conditions and it is not intended for such use.

6. Guidelines Including the Use of the Medicine in Relation with the Proposed Indications

Below are presented some of the available guidelines for the treatment and management of hypertension and heart failure.

- National Clinical Guideline Center (NCGC): Hypertension - 2011
  http://www.nice.org.uk/nicemedia/live/13561/56007/56007.pdf
- European Society of Hypertension: Guidelines for the Management of Arterial Hypertension - 2007
  http://www.escardio.org/guidelines-surveys/esc-guidelines/guidelinesdocuments/guidelines-ah-ft.pdf
- National Heart, Lung, and Blood Institute (NHLBI): The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure - 2004
  http://www.nhlbi.nih.gov/guidelines/hypertension/index.html

7. Intervention and Summary of Evidence

The indications specified in the clinical questions presented below are based on input from the PAHO technical unit supporting this request (NMH/ND) and the evidence presented in this section was obtained in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb).

For chlorthalidone, the intervention and summary evidence has been compiled in one table, with the corresponding tables.

The search strategy and references supporting the intervention and summary of evidence are available in *Section 9* of this dossier.

7.1 Chlorthalidone Versus Hydrochlorothiazide in Adults with Hypertension or Heart Failure

CLINICAL QUESTIONS
What is the compared efficacy and safety of chlorthalidone versus hydrochlorothiazide in adults with hypertension? What is the compared efficacy and safety of chlorthalidone versus hydrochlorothiazide in adults with heart failure?

CONTEXT	Chlorthalidone versus hydrochlorothiazide
In 2004, the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNS7) advocated the use of "thiazide-type diuretics as the preferred initial agent". JNC7 mentioned two thiazide-type diuretics, hydrochlorothiazide (HCTZ) and chlorthalidone (CTDN), but expressed no preference of one over the other. The pharmaceutical presentation of the two drugs differs. HCTZ is available in 12.5mg and 25.0mg tablets and 19 fixed-dose combinations, whereas CTDN is available in 25mg tablets and in only three fixed-dose combinations. Because of the availability of more presentations of HCTZ, it is the most frequently prescribed. Over the last years, some studies have discussed the differences of these drugs pharmacologically and recommended CDTN over HCTZ. Two recent reanalyses of Multiple Risk Factor Intervention Trial (MRFIT) data found CDTN superior to HCTZ in reducing cardiovascular events (CVEs) and left ventricular hypertrophy. However, no randomized controlled trials compared the two medications head to head with respect to CVEs.	

INTERVENTION	Chlorthalidone versus hydrochlorothiazide
Chlorthalidone compared to hydrochlorothiazide does not differ in reducing all-cause mortality. Low quality evidence.	
Chlorthalidone compared to hydrochlorothiazide does not differ in reducing stroke. Low quality evidence.	
Chlorthalidone compared to hydrochlorothiazide reduces the incidence of congestive heart failure. Moderate quality evidence.	
Chlorthalidone is superior to hydrochlorothiazide in reducing the incidence of cardiovascular events. Moderate quality evidence.	
Chlorthalidone compared to hydrochlorothiazide does not differ in reducing office systolic blood pressure. Low quality evidence.	
Chlorthalidone compared to hydrochlorothiazide has a higher risk of hospitalization for hypokalemia or hyponatremia. Moderate quality evidence.	

Summary of evidence	
Benefits	A systematic review (9 RCTs) with a network meta-analysis (4 RCTs) was found (*1*). As there is no head to head comparison of chlorthalidone compared to hydrochlorothiazide, the Table 1 outlines the main characteristics of the studies considered. The trials assessed a series of cardiovascular events (all-cause mortality; stroke; CHF: congestive heart failure; CVEs: cardiovascular events) defined in the Table 2. Another outcome considered was the office systolic baseline blood pressure difference (OSBP). The OSBP was defined as the mean achieved OSBP in the diuretic arm minus the mean achieved OSBP in the nondiuretic arm. The RR for CVEs for the diuretic versus its nondiuretic comparators was modeled by including the OSPD difference, a continuous variable, along with the dichotomous diuretic variables, with values of 1 and 0, corresponding with HCTZ and CTDN, respectively. The studies included into the network meta-analysis were: ALLHAT (*2,3*), examining CDTN versus lisinopril or amlodipine, and the Second Australian National Blood Pressure (ANBP2) Study (*4*), examining HCTZ versus enalapril. Finally ACCOMPLISH (5-*7*), compared HCTZ versus amlodipine. The studies included patients with hypertension and in general terms had a high cardiovascular risk, but the trials did not report disaggregated results for patients with heart failure. The demographic features, risk factors and co-morbidities of each study are show in the Table 3. The results from the network meta-analysis showed that CTDN compared to HCTZ reduced the episodes of congestive heart failure (4 RCTs, RR 0.77, 95% CI 0.61 to 0.98; P=0.032) and cardiovascular events (4 RCTs, RR 0.79, 95% CI 0.72 to 0.88, P<0.0001). The differences for all-cause mortality and stroke, were not statistically significant different (4 RCTs, RR 0.94, 95% CI 0.82 to 1.09, RR 0.96, 95% CI 0.76 to 1.21; respectively). Based on expected events in the HCTZ arm of the ANBP2 study the number of patients needed to treat to prevent 1 CVE with CDTN rather than HCTZ over 5 years was 27. On the other hand, the RR for CVEs versus the difference in mean achieved OSPD between the diuretic and nondiuretic arms in each trial was not statistically significant different (p=0.849).
Risks	No systematic reviews were identified studying the safety of CDTN versus HCTZ. We identified a propensity score-matched observational cohort study with up to 5 years of follow up (8), and two clinical trials (*2,5*) included in the network meta-analysis (*1*). The Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic (ALLHAT) study included 33357 participants, aged 55 years or older, with hypertension and at least one other coronary heart disease risk factor from 623 North American centers. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial that included 11506 patients with hypertension, who were at high risk for cardiovascular events. The patients received treatment with benazepril plus amlodipine or benazepril plus hydrochlorothiazide. Results from ALLHAT clinical trial showed that six-year rates of hospitalization for gastrointestinal bleeding, available only in Medicare and Department of Veterans Affairs participants, occurred in 8.8%, 8.0%, and 9.6% participants in the chlorthalidone, amlodipine, and lisinopril treatment groups, respectively. No significant differences were found between the groups (amlodipine versus chlorthalidone, RR 0.92, CI95% 0.82 to 1.03; p=0.15; lisinopril versus chlorthalidone, RR 1.11, CI95% 0.99 to 1.24; p=0.07). No differences were found in the ACCOMPLISH trial between benazepril-amlodipine group and benazepril hydrochlorothiazide regarding hyperkalemia, hypokalemia or hypotension. The retrospective population-based cohort study of residents of Ontario, Canada, included patients aged 66 years or older, who initiated chlorthalidone or hydrochlorothiazide therapy between 1 January 1993 and 31 March 2010. The primary outcome was a composite of death or hospitalization with acute myocardial infarction, heart failure, or ischemic stroke, all of which might be consequences of inadequately treated hypertension. The safety outcomes were hospitalization with hypokalemia or hyponatremia This study showed that patients with hypokalemia were hospitalized at a rate of 0.69 events per 100 person-years of follow-up in the chlorthalidone group compared with 0.27 events per 100 person-years of follow-up in the hydrochlorothiazide group (adjusted HR 3.06 (CI 95%, 2.04 to 4.58). Patients treated with chlorthalidone also showed a higher risk of hospitalization due to hyponatremia (adjusted HR 1.67 (CI95% 1.25 to 2.23)).

Comments/ Applicability	The results from the network meta-analysis showed a relative reduction of 21% in the risk of cardiovascular events of chlorthalidone over hydrochlorothiazide. From the authors' point of view, the apparent superiority of chlorthalidone should be reflected in the availability of more pharmaceutical preparations in terms of dosage and combinations with other antihypertensive drugs to balance the availability of hydrochlorothiazide preparations. Despite of this, the lack of data from head to head comparisons limits the applicability of the available evidence to decide if any of these thiazide-type diuretics could be preferred over the other. Although the results of the network meta-analysis assessed in these two clinical questions allow drawing some conclusions about the superiority of chlorthalidone, it should to be noted that this conclusion is based on indirect evidence limiting the confidence in the effect estimates available. The lack of disaggregated data for patients with heart failure also limits the applicability of the results.
	The applicability of these results also should be considered in the light of other issues related to their validity, as the "effect modification", related to population-drug interactions (e.g. ACE inhibitors in black patients), that might be the major source of bias in the comparisons performed in the network meta-analysis. In that sense, the ALLHAT trials included a higher number of black patients that the Second Australian National Blood Pressure Study, but the review authors minimized this bias by restricting a drug-adjusted analysis to white patients from the ALLHAT data and by obtaining an indirect comparison of both drugs ($RR_{CDTN/HCTZ}$) in the OSBP-adjusted analysis.
	Other potential sources of bias were the differences in definitions of CVEs in the considered trials, and the early termination of both ACCOMPLISH and ALLHAT trials.
Cost studies	Direct information about cost studies that included chlorthalidone and hydrochlorothiazide were not found. A publication reported data on cost-effectiveness of chlorthalidone, amlodipine, and lisinopril as first line treatments for hypertension, based on data from the ALLHAT trial (10). The treatments were ranked by increasing cost and compared the cost-effectiveness between the lowest cost strategies with the strategy that has the next highest cost. Cost-effectiveness was calculated as the difference in the cost divided by the difference in life years (LYs) by the formula $CE= [Cost_{Drug\ A} - Cost_{DrugB}]/ [LY_{Drug\ A} - LY_{DrugB}]$. A similar analysis was performed using quality – adjusted LYs (QALYs). To evaluate the uncertainty in the incremental cost-effectiveness ratios, the analysis was repeated for 500 boot-strapped samples. The sensitivity analysis included relative risk of death, quality of life, drug cost per day, and cost of office visits. It is important to note that chlorthalidone was used as a control in these analyses. In contrast to amlodipine and lisinopril, chlorthalidone was in all the scenarios the least expensive medicine (on average US$ 4,802 less than amlodipine, and US$ 3,700 less than lisinopril). Amlodipine provided more LYs than chlorthalidone in 84% of boot-strapped samples (mean 37 days) at an incremental cost-effectiveness ratio of US$ 48400 per LY gained. Lisinopril provided fewer LYs than chlorthalidone in 55% boot-strapped samples (mean 7-day loss) despite a higher cost. At a threshold of US$ 50,000 per LY gained, amlodipine was preferred in 50%, chlorthalidone in 40%, and lisinopril in 10% of boot-strapped samples. However, these findings were highly sensitive to the costs of amlodipine and the chosen cost-effectiveness threshold. Initial treatment with chlorthalidone is less expensive than lisinopril or amlodipine, but amlodipine provided a no significantly greater survival benefit and might be a cost-effective alternative.

Table 1. Study, Year of Publication, Location, Size, Base Drug, and Step Drugs

Study/Year Published	Site	N	Diuretic Arm	Nondiuretic Arm, Dose in mg	Step Drugs If Needed to Achieve BP Goal (Applied to Both Arms Unless Otherwise Specified)
HCTZ TRIALS					
Oslo/1980 (*11*)	Oslo population sample	785	HCTZ 50	Usual care	Diuretic arm only: methyldopa or, if adverse effects, propranolol
ANBP2/2003 (*4*)	Australian practices	6083	HCTZ dose Per physician	Enalapril, dose per physician	2: β-blockers, α-blockers, calcium channel blockers
ACCOMPLISH/ 2008 (*5-7*)	US and Nordic centers	11506	HCTZ 12.5-25.0 plus benazepril 20-40	Amlodipine 5-10 plus Benazepril 20-40	2: β-blockers, α-blockers, clonidine, spironolactone
CTDN TRIALS					
HDFP/1979, 1979, 1982, 1984 (*12-15*)	US communities	10940	CTDN 25-100	Referred care	Diuretic arm only: 2: reserpine or methyldopa; 3: hydralazine; 4: guanethidine
SHEP/1991 (*16*)	US centers	4736	CTDN 12.5-25.0	Placebo	2: diuretic arm: atenolol or reserpine 2: placebo arm: matching placebo
ALLHAT/2002 (*2,3*)	No. American centers	24309*	CDTN 12.5-25.0	Lisinopril 10-40	2:atenolol, reserpine, clonidine 3: hydralazine
ALLHAT/2002 (*2,3*)	No. American centers	24303*	CDTN 12.5-25.0	Amlodipine 2.5-10.0	2: atenolol, reserpine, clonidine 3: hydralazine
ALLHAT/2003 (*17*)	No. American centers	24335*	CDTN 12.5-25.0	Doxazosin 2-8	2: atenolol, reserpine, clonidine 3: hydralazine
SHELL/2003 (*18*)	134 Italian practices	1882	CDTN 12.5-25.0	Lacidipine 4-6	2:fosinopril

ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ACCOMPLISH, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; ANBP2, Second Australian National Blood Pressure Study; HCTZ, hydrochlorothiazide; CTDN, chlorthalidone; SHELL, Systolic Hypertension in the Elderly long-Term Lacidipine Trial; SHEP, Systolic Hypertension in the Elderly program; HDFP, Hypertension Detection and Follow-Up Program.
*CTDN, lisinopril, amlodipine, and doxazosin arms were allocated 15255, 9048, 9054, and 9061, respectively (total=42418)

Table 2. Definition of Cardiovascular Events (CVEs) in the Included Studies

Study	Heart failure	Coronary events	Other cardiac events	Stroke	Other events
HCTZ Trials					
Oslo	Heart failure	MI	"Fatal myocarditis"	Stroke	NS
ANBP2	Heart failure	Coronary events associated with, revascularizations, coronary deaths	Sudden or rapid death from cardiac causes, death from noncoronary cardiac causes	Stroke, TIA	Occlusion of any other major artery, death from other vascular causes, dissecting or ruptured aortic aneurysm
ACCOMPLISH	Heart failure	MI, coronary revascularization, hospitalization for unstable angina	Sudden death from cardiac causes, resuscitation after Sudden cardiac arrest	Stroke	Death from other cardiovascular causes
CDTN Trials					
HDFP	NS	MI, Angina	NS	Stroke	NS
SHEP	NS	MI, angina, coronary revascularization	Sudden cardiac death, rapid cardiac death	Stroke, TIA	Aneurysm, endarterectomy
SHELL	Heart failure	MI	NS	Stroke	Sudden death, endarterectomy
ALLHAT	Heart failure	MI, coronary revascularization, hospitalized or treated angina, fatal CHD	NS	Stroke	PAD revascularization

NS: Not specified; MI: myocardial infarction; CVA: stroke; TIA: transient ischemic attack; PAD: peripheral arterial disease

Table 3. Demographic Features, Risk Factors and Co-Morbidities at Baseline

Study Step 1 comparison	Mean age	Mean BMI	Percent with Characteristic						
			Women	Black	Smokers	Diabetes	MI or CHD	CVA	MI or CVA
Oslo HCTZ vs Usual Care	45	26	0	NA	42	0	0	0	0
ANBP2 HCTZ vs enalapril	72	27	51	≤5	7	7	8	5	NA
ACCOMPLISH HCTZ vs Amlodipine	68	31	40	12	11	60	24	13	NA
HDFP CTDN vs referred care	51	NA	46	44	26	7	5	3	NA
SHEP CTDN vs placebo	72	28	56	14	13	10	5	1	NA
ALLHAT CTDN vs lisinopril	67	30	47	32	22	36	NA	NA	23
ALLHAT CDTN vs amlodipine	67	30	47	32	22	36	NA	NA	23
ALLHAT CDTN vs doxazosin	67	30	47	32	22	36	NA	NA	23
SHELL CTDN vs Lacidipine	72	NA	61	NA	11	13	NA	NA	NA

NA: Not available; CVA: stroke; CHD: coronary heart disease; MI: myocardial infarction; BMI: body mass index

Table 4. GRADE Evaluation of Clinical Outcomes (Assessment for all the Outcomes from Data in Reference 1)

Number of studies (N))	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
4 (50.946)	All-cause mortality	CTDN HCTZ	4	0	0	-1	-1	Low	Data available from indirect evidence, no head to head studies comparing chlorthalidone and hydrochlorothiazide. Wide confidence intervals.
4 (50.946)	Stroke	CTDN HCTZ	4	0	0	-1	-1	Low	Data available from indirect evidence, no head to head studies comparing chlorthalidone and hydrochlorothiazide. Wide confidence intervals.
4 (50.946)	Congestive heart failure	CTDN HCTZ	4	0	0	-1	0	Moderate	Data available from indirect evidence, no head to head studies comparing chlorthalidone and hydrochlorothiazide
4 (50.946)	Cardiovascular events	CTDN HCTZ	4	0	0	-1	0	Moderate	Data available from indirect evidence, no head to head studies comparing chlorthalidone and hydrochlorothiazide
4 (50.946)	Office systolic baseline blood pressure	CTDN HCTZ	4	0	0	-1	-1	Low	Data available from indirect evidence, no head to head studies comparing chlorthalidone and hydrochlorothiazide. Wide confidence intervals.
1 (29.873)	Safety (hospitalization with hypokalemia or hyponatremia)	CTDN HCTZ	2	0	+1	-1	-1	Moderate	Observational study with strong estimate of effects, consistent after adjustment to the main confounding factors.

Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic/expert opinion

8. Special Considerations and Additional Comments (*9-18*)

8.1 Regulatory Status of the Product in National Regulatory Authorities (NRAs)

The following table reflects the regulatory status of the product (innovator and generic – if applicable) in the 7 PAHO Region Reference NRAs (Argentina, Brazil, Canada, Colombia, Cuba, Mexico and United States) and the European Medicine Agency.

NRA	Status	
	Innovator	Generic
Argentina (ANMAT)	---	x
Brazil (ANVISA)	x	x
Canada (Health Canada)	---	x
Colombia (INVIMA)	---	---
Cuba (CECMED)	---	---
Mexico (COFEPRIS)	---	x
USA (FDA)	---	x
Europe (EMA)	---	---

8.2 PAHO Member State Prices

Through ECONMED (an electronic listserv for public officials from the health sector), PAHO requested the price paid for procurement of Chlorthalidone from Member States who utilize this products in their National Public Health Programs. Unfortunately, no data has been provided to PAHO by countries in Latin America and the Caribbean. PAHO will increase efforts to obtain some prices from Member States and will distribute the information when the committee convenes in Washington, D.C.

8.3 Results of PAHO Expression of Interest

For a medicine to be eligible for inclusion in the PAHO Strategic Fund medicine list, it must have supporting evidence of safety, efficacy, and clinical effectiveness. Additionally the product must satisfy one of the following criteria as related to the pharmaceutical market:

1. The acquisition of the medicines is subject to particular challenges related to product procurement, pricing, patent status, forecasting of future needs, and exclusivity contracts between pharmaceutical companies that restrict marketing in specific geographical areas.
2. Leveraging economies of scale (increases in the volume of medicine procured) can result in lower costs.

PAHO has established this criteria to ensure the inclusion of the product in the Strategic Fund will provide value added to Member States who procure this product through PAHO.

To evaluate these pharmaceutical market factors, the Procurement (PRO) Unit of PAHO conducted an Expression of Interest (EoI) to gather information related to the product. PRO contacted 19 suppliers, which are included in the PAHO approved supplier list, and asked for product data (i.e. available presentations, manufacturing origin & capacity, potential restrictions, prices, and available technical documents).

Limited response was obtained from the contacted suppliers; however, PRO believes chlorthalidone, does meet the pharmaceutical market criteria. Nonetheless, significant challenges are present and the following are key recommendations:

- Consolidate regional demand to leverage the benefits of economies of scale. If PAHO is able to obtain sufficient demand perform an international tender and establish Long Term Agreements with suppliers.
- Increase number of PAHO approved suppliers offering this product in order to ensure availability and create a more competitive market.

8.4 Potential Value Added for Procurement of the Medicine through the Strategic Fund

Chlorthalidone is not an expensive thiazide diuretic (reference price of US$ 0.0397 per unit in 2011); however, it is utilized as a first-line therapy in the treatment and management of hypertension and heart failure according to various clinical guidelines. Presently, the Strategic Fund list has only one thiazide diuretic, hydrochlorothiazide, as part of its cardiovascular medicines and may limit options in treatment of patients.

If the presented evidence demonstrates adequate safety, efficacy, and clinical effectiveness, PAHO believes the inclusion of this product will improve Member States access to an effective and safe medicine that can be used as a first line therapy or an alternative to treat hypertension and heart failure. Additionally, PAHO would aim to consolidate regional demand to lower the costs of the product, thus easing the financial burden on Member States.

9. Search Strategy and References Supporting Intervention and Summary of Evidence

9.1 Inclusion Criteria

The aim of this evidence summary is to gather information from a systematic review about the benefits and risk of a drug in a specific health problem. For this reason we include in the summary the results from a rigorous systematic review, prioritizing Cochrane reviews. When a Cochrane review is not available or it is not suitable to respond the scope of the clinical question, we consider the inclusion of a systematic review that at least: i) includes a clearly defined inclusion criteria; ii) reports a recent search in at least two databases; and iii) reports any efforts from authors to assess the risk of bias from the included studies.

These criteria are the minimum requirements established by the Centre for Reviews and Dissemination to include a systematic review in the Database of Abstracts of Reviews of Effects (DARE; www.crd.york.ac.uk/crdweb/AboutPage.asp). For the specific purposes of the "Cost studies" section we include the results from an economic evaluation, that is; a comparison of two or more interventions or care alternatives (including cost-benefit analyses, cost-utility analyses, and cost-effectiveness analyses).

9.2 Search for Studies

The inclusion criteria described above determines the search for the studies planned. We design specific search algorithms to search the AHRQ Effective Health Care Program and The Cochrane Library as the main source to retrieve high quality systematic reviews. Each search in these two resources is complemented with a search in MEDLINE (accessed through PubMed) with the purpose of check any additional or more recent systematic review. The search is performed without any limitation, with the exception of PubMed in which we limit the search to the validated subset of systematic reviews (systematic[sb]). As we included only economic

evaluations in the "Cost studies" section we limit the search to the NHS EED Database. In those cases that the NHS EED Database does not provide relevant results, we perform a specific search in MEDLINE, limiting the search algorithm designed to retrieve systematic review with the term cost*[tiab]. The search to develop the present clinical question was performed in May 2013, with the search strategies detailed below (Section 9.5).

9.3 Rating the Quality of the Evidence

Each evidence summary provides a rating of the quality of evidence following the GRADE guidance. GRADE specifies four categories (high, moderate, low, and very low) that are applied to the body of evidence that supports each assessed outcome. In the context of a synthesis of the evidence the quality of evidence reflects the confidence that the estimates of the effect are correct. For each clinical question one experienced researcher collects in a table the number of studies and patients included in these studies that set the body of evidence for each specific outcome discussed in the "Benefits" and "Risks" sections. The quality of evidence is then rated for each specific outcome and a final category is provided, commenting the main limitations that compromise the quality of evidence. All the information collected in the table, and the details required to the rating of the quality of evidence are obtained from the assessed systematic review used to develop the evidence summary.

9.4 Selection Criteria

One experienced researcher screens the results from the search applying the inclusion criteria commented above. If a Cochrane review is identified, it is selected to develop the evidence summary. When a Cochrane review is not suitable to respond to the scope of the formulated clinical question, the references from MEDLINE are screened. For the purposes of this clinical question, no Cochrane reviews were available and from the 9 references obtained in MEDLINE only the assessed systematic review (*1*) fulfilled with the inclusion criteria mentioned above.

9.5 Search Strategy Results

The search to develop the present clinical question was performed in May 2013, with the following search strategies:

- Agency for Healthcare Research and Quality – Effective Health Care Program
  http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/
  chlorthalidone 0 hits
- The Cochrane Library (Issue 3 of 12, March 2013)
  chlorthalidone:ti,ab,kw 508 hits
- MEDLINE (accessed via PubMed)
  chlorthalidone[tiab] AND hypertension[ti] AND systematic[sb] 9 hits

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10. Additional References

The following references are those cited in Section 2 (Public Health Relevance), Section 4 (Medicine Characteristics and Pharmacological Information) and Section 8 (Special Considerations and Additional Comments). References supporting the intervention and summary of evidence are available in Section 9.6.

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Annex 2

Review of the Available Evidence of Clopidogrel 75mg Tablet for Potential Inclusion in the Pan American Health Organization Strategic Fund Medicine List

Annex 2: Table of Contents

1. Introduction to the PAHO Strategic Fund

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (Strategic Fund) was created by the Director of the Pan American Health Organization (PAHO) at the request of Member States of the Organization, in September 1998 during the 35th session of the Pan American Sanitary Conference.

The Strategic Fund is a regional mechanism which aims to strengthen the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe and effective supplies at affordable prices obtained by leveraging the advantages of economies of scale.

To accomplish this objective the Strategic Fund publishes a list of medicines available for procurement in name of the Organization's Member States. The list utilizes as a foundation the World Health Organization (WHO) Essential Medicines List (EML); however, recently there has been a significant increase in Member State requests to procure products not included in the WHO EML.

In order to meet the needs of PAHO Member States the PAHO Director has created an external Expert Committee to review requests for inclusion of medicines not included in the WHO EML. This Expert Committee will allow PAHO to implement a decision making mechanism in agreement with concepts of quality, efficacy, safety and when available, information related to the value they provide in relation to their cost.

The committee will work exclusively on requests to update the SF medicine list, which will enable PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this EC should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

2. Public Health Relevance (*1-3*)

2.1 NCDs in the Region of the Americas

Over the last decades, noncommunicable diseases (NCDs) have become the leading cause of morbidity and mortality across the globe while imposing a growing threat to international development goals and economic growth as well as contributing to dramatic rises in health care expenditures.

The main NCDs principally include cardiovascular disease, cancer, diabetes and respiratory diseases and are accompanied by various common risk factors rising at a rapid pace. In the Americas region, NCDs are responsible for 3 out of every 4 deaths with cardiovascular diseases and cancer as the leading causes responsible respectively for 1.9 million and 1.2 million deaths each year. More than one third of these deaths are premature and occur in people under the age of 70 years old therefore leading to serious repercussions on social and economic development.

Noncommunicable diseases not only slow down development but also place a heavy financial burden on patients, healthcare and governments. The costs to overall health systems are expect to rise as governments are expected to increase funding to prevent and treat these diseases. Confronting the rising costs constitutes a real challenge in low and middle income countries of the Americas where economic growth is often compromised and healthcare systems have to manage access and equity issues. Patients are facing similar issues, as in many countries healthcare costs are paid out-of-pocket and the impact of NCDs on household budgets and healthcare expenditures can often lead to catastrophic spending and impoverishment.

In some countries of the region, out-of-pocket expenditures account for 78% of spending on medicines. Cardiovascular diseases constitute an important family expenditure on healthcare and can become an enormous economic and social burden in low-and-middle income countries. For example, patients suffering from more than two chronic diseases and taking more than two medicines for these conditions account for 10% of all patients in some countries. Health expenditures for this population can reach 50% of the overall health expenditure. Hence, in Latin America, out-of-pocket expenses related to NCDs and health expenditures accounting for chronic diseases represent a critical health care and financial issue.

In response to the NCD situation in the Americas, the 28th Pan American Sanitary Conference in September 2012, adopted the Regional Strategy for the Prevention and Control of Noncommunicable Diseases (Resolution CSP28.R13 aims to:

> "reorient and strengthen health systems to improve coverage, access to and quality of care provided to the people with NCDs or their risk factors, based on primary health care"

This process is linked with the WHO voluntary global NCD targets for 2025, which aims to achieve the following:

- 25% relative reduction of premature mortality due to noncommunicable diseases
- 80% coverage of essential NCD medicines and technologies
- 50% coverage of drug therapy and counseling.

As a critical component of PAHO's response to these issues, the Strategic Fund is increasing support and assistance to Member States by amplifying the list of NCD medicines for countries to procure. Thus, increasing access to quality drugs and helping ease the increasing financial burden, specifically for new or high cost medicines.

The Strategic Fund has initiated a process to review the available evidence regarding the efficacy, safety and cost-effectiveness of NCD medicines, particularly for cardiovascular diseases and cancer. The following document presents the status of the medicine, basic pharmacological information, the evidence comparing the requested medicine and its alternative for the specified indications and other relevant information.

2.2 Cardiovascular Health Situation in the Americas

Cardiovascular diseases (CVD) are the main leading cause of death globally and accounts for 30% of deaths annually worldwide. In 2007, cardiovascular diseases caused 1.5 million deaths in the Region of the Americas where approximately 40% occur prematurely at an early stage of productive life. Among risk factors such as obesity, hypercholesterolemia and smoking, hypertension is the greatest risk factor for CVD and accounts for 62% of strokes and 49% of ischemic heart disease. Recent data states 18% of the adult population in Latin America suffers from hypertension. Therefore, the control of hypertension becomes the central focus in reducing cardiovascular disease risk.

Early detection and effective pharmacological treatments are crucial in order to reduce hypertension incidence and prevalence among the Region's population, but also to prevent further consequences such as stroke, acute coronary syndrome, congestive heart failure, and others. In low and middle income countries such as in the Americas, the best evidence-based approach for CVDs is a multidrug combination (aspirin, two antihypertensive medicine, and statins) for patients at high risk of cardiovascular disease or who already had a past cardiovascular event.

Considering these diseases and risk factors are more prevalent among poor populations and affect to a greater extend the vulnerable and socially disadvantaged, PAHO aims to increase access to quality medicines to prevent and treat cardiovascular diseases and decrease the financial burden they can represent.

3. Entity Supporting the Application and Requested Indications

3.1 Entity Supporting Application

The PAHO Noncommunicable Diseases and Disabilities Unit (NMH/ND) is requesting and supporting this application.

3.2 Requested Indications

Clopidogrel, a platelet aggregation inhibitor, has been requested for the prevention of atherothrombotic events for patients with recent myocardial infarction, stroke, peripheral arterial disease, acute coronary syndrome or atrial fibrillation.

4. Medicine Characteristics and Pharmacological Information (*4-10*)

4.1 General Information

1) Medicine name (INN)	Clopidogrel
2) ATC (anatomical therapeutic chemical - WHO Drug classification system)	B01AC04
3) Reference trade name: (1. Innovator & 2. Generic - when available some examples provided)	1. Innovator: Plavix (Sanofi Pharma Bristol-Myers Squibb SNC) 2. Generic: Clopidogrel Bisulfate (Mylan Pharms Inc) Clopidogrel Bisulfate (Apotex Inc)
4) Therapeutic class (according to classification in the WHO EML)	This medicine is not present in WHO EML. The pharmacological class is platelet aggregation inhibitor or antiplatelet.

4.2 Mechanism of Action

Clopidogrel inhibits selectively platelet activation and aggregation through the Irreversible binding of its active metabolite to the P2Y12 class of adenosine diphosphate (ADP) receptors on platelets.

4.3 Pharmacokinetic Considerations

Clopidogrel is a drug that is metabolized to a pharmacologically active metabolite and inactive metabolites.

- *Absorption:* Rapid absorption. Bioavailability (≥50%); Tmax=30-60 min.
- *Effect of food:* Clopidogrel can be administered with or without food, bioavailability is not altered.

- *Distribution:* Clopidogrel and its inactive metabolite bind reversibly in vitro to human plasma proteins (98% and 94% respectively). The binding is non-saturable.
- *Metabolism:* Hepatic (extensive) via CYP450 2C19, 3A4, 2B6 and 1A2 (active thiol metabolite) and hydrolysis (inactive carboxylic acid derivative).
- *Elimination:* Urine (50%), feces (46%); After a single oral dose:T1/2=6 hrs (clopidogrel), 30 min (active metabolite). Elimination T1/2=8 hrs for the main inactive circulating metabolite.

4.4 Pharmacodynamic Considerations

Platelets exposed to clopidogrel's active metabolite are affected for the remainder of their lifespan (7-10 days). With daily dosing of 75mg, the inhibition reaches steady state between day 3 and 7 (average inhibition 40-60%). Platelet aggregation and bleeding time return to baseline values once treatment is discontinued in approximately 5 days.

4.5 Pharmacogenomic Considerations

CYP2C19 is involved in the formation of clopidogrel's both active and intermediate metabolite. Thus, clopidogrel's antiplatelet effect can be altered by genetic variation of CYP450. Poor CYP2C19 metabolism (2% whites, 4% black and 14% Chinese) can result in less active metabolite and reduced platelet aggregation inhibition. Clinical outcomes can be resumed as increased risk of cardiovascular events (myocardial infarction, stroke, death) or stent thrombosis for this genotype. Tests are available to determine a patient's 2C19 genotype.

4.6 Use in Specific Populations

- *Pregnancy:* Category B. There is no evidence of embryotoxicity of teratogenicity in animal studies however no adequate and well-controlled studies have been done in pregnant women. Clopidogrel should not be used in women during pregnancy.
- *Lactation:* Animal studies have proved that clopidogrel and/or metabolites are excreted in animal milk. It remains unknown if clopidogrel is excreted in human breast milk. Avoid clopidogrel if breastfeeding.
- *Fertility:* Clopidogrel did not alter fertility in animal studies.
- *Pediatric use:* Safety and effectiveness in pediatric populations have not been established therefore use of clopidogrel is not recommended.
- *Geriatric use:* No dosage adjustment required (no difference in platelet aggregation and bleeding time in the elderly).
- *Renal impairment:* Limited experience in patients with moderate to severe renal impairment (inhibition of platelet aggregation may be lower).
- *Hepatic impairment:* No dosage adjustment required but caution required.
- *Gender:* Possibly less inhibition of platelet aggregation in women (based on small study).

4.7 Dosage, Preparation and Administration

- *Dosage and Administration:*
  - Film-coated tablet, 75mg, contains clopidogrel bisulfate, for oral administration.
- *Acute coronary syndrome (ACS):*
  - For patients with non ST elevation ACS (unstable angina/non-Q-wave myocardial infarction (MI) initiate clopidogrel at 300mg oral loading dose then continue at 75mg once daily in combination with aspirin (75-325mg once daily) *since clinical trials demonstrated a higher risk of bleeding with high aspirin, the aspirin dose should not be higher than 100mg. The optimal duration of the therapy has been established to 12 months.
  - For patients with STEMI (ST segment elevation myocardial infarction) the recommended dose is 75mg once daily orally in combination with aspirin (75-325mg once daily), with or without thrombolytics. Clopidogrel can be initiated with or without loading dose (300mg).
- *Recent MI, recent stroke, or established peripheral arterial disease:*
  - Recommended dose of clopidogrel is 75mg once daily orally.
- *Atrial fibrillation:*
  - Recommended dose for 75mg once daily orally in combination with aspirin (75-100mg once daily); for patients unsuitable for anticoagulation therapy with at least one risk factor of vascular event and at low risk of bleeding; indicated for the prevention of atherothrombotic and thromboembolic eve0.1944 innts, including stroke.

4.8 Contraindications

- Active pathological bleeding (peptic ulcer, intracranial hemorrhage)
- Hypersensitivity (e.g.: anaphylaxis) to clopidogrel (active substance) or any component of the product (excipients)
- Severe hepatic impairment

4.9 Warnings/Precautions

- *General risk of bleeding:*
  - Caution if elective surgery planned within 5 days. Clopidogrel should be discontinued 5 to 7 days prior to surgery to avoid increased risk of bleeding and allow reversal of its effect.
- *Recent ischemic stroke:*
  - Because of lack of data, clopidogrel cannot be recommended during the first 7 days following an acute ischemic stroke.
- *Reduced antiplatelet activity due to impaired CYP2C19 function:*
  - Clopidogrel is a pro drug. The antiplatelet activity is due to its active metabolite. Impairment of the drug's metabolism through CYP2C19 can result in reduced active metabolite concentration and in diminished antiplatelet activity. Caution is required if poor or intermediate CYP2C19 metabolizers. Also, avoid concomitant use with proton pump inhibitor (PPI) omeprazole and esomeprazole because of resulting 2C19 inhibition that can affect antiplatelet activity. If a PPI has to be used, con-

sider one with less 2C19 inhibition such as pantoprazole for example. As a precaution, any other drug with a moderate to strong potential to inhibit 2C19 should be administered with caution.

- *Discontinuation of clopidogrel:*
  - Caution if therapy must be interrupted or discontinued because it increases risk of cardiovascular events. If therapy must be temporarily discontinued, restart as soon as possible.
- *Hematological disorders:*
  - Thrombotic Thrombocytopenic Purpura (TTP) has been reported but very rarely. Caution if characteristics of TTP such as thrombocytopenia, microangiopathic hemolytic anemia, neurological findings, renal dysfunction, and fever arise. TTP is a potentially fatal condition. Blood cell count and appropriate testing should be considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment.
- *Renal impairment:*
  - Caution if severe or moderate renal impairment as therapeutic experience with clopidogrel is limited in such patients.
- *Hepatic impairment:*
  - Caution if clopidogrel is used in patients with moderate to severe hepatic impairment, as therapeutic experience is limited. Liver function should be carefully monitored.

4.10 Side Effects

Common	Serious and rare:
• Bleeding • Gastrointestinal hemorrhage • Bruising • Hematoma • Epistaxis • Headache • Dizziness • Nausea/vomiting/diarrhea • Dyspepsia • Abdominal pain	• Blood disorders (agranulocytosis/ granulocytopenia, neutropenia, severe thrombocytopenia, thrombotic thrombocytopenic purpura (TTP) and aplastic anemia) • Bleeding: Intracranial bleeding, eye bleeding, skin bleeding (purpura), respiratory tract bleeding, etc. • Gastrointestinal disorders: duodenal, gastric or peptic ulcer, gastritis, pancreatitis, stomatitis • Skin disorders: rash, bullous dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, etc. • Other serious and rare side effects reported in NRA monographs

4.11 Main Interactions

Drug	Interaction
Proton pump inhibitors	Avoid use of omeprazole and esomeprazole (CYP2C19 inhibitors) as it may reduce platelet inhibition, other PPIs can be used.
NSAIDs/ASA	Can increase risk of gastrointestinal bleeding *NOTE that clopidogrel and ASA have been administered together up to one year, concomitant use should be undertaken with caution .
Warfarin	Can increase risk of bleeding
Heparin, thrombolytics, glycoprotein IIb/IIIa inhibitors	These pharmacodynamic interactions do not decrease clopidogrel's efficacy but can increase risk of bleeding, use with caution
Strong or moderate inhibitors of 2C19 (omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol)	The relevance of this interaction is uncertain and may vary according to each drug. Products that inhibit CYP2C19 can affect antiplatelet activity therefore their use is discouraged.

4.12 Other

- *Storage*
  - 25° C (77°F) but can be stored between 15° C and 30° C, protect from moisture
- Patients should inform dentists and physicians that they are taking clopidogrel prior to surgery or intervention that could increase the risk of bleeding

5. Alternatives to Clopidogrel Available in the Strategic Fund

There is presently no alternative in the Strategic Fund medicine list; however, acetylsalicylic acid is an alternative present on the WHO EML list.

The following document provides the supporting evidence regarding the comparison of clopidogrel used as a single agent or in combination with aspirin versus aspirin or warfarin, dependent on the indication. This document does not represent a therapeutic guideline for treatment of these conditions and it is not intended for such use.

6. Guidelines Including the Use of the Medicine in Relation with the Proposed Indications

Below are presented some of the available guidelines for the treatment and management of cardiovascular diseases.

- European Society of Cardiology (ESC): European Guidelines on cardiovascular disease prevention in clinical practice – 2012
  http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-CVD-prevention.pdf

7. Intervention and Summary of Evidence

The indications specified in the clinical questions presented below are based on input from the PAHO technical unit supporting this request (NMH/ND) and the evidence presented in this section was obtained in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb).

For clopidogrel, the intervention and summary evidence has been compiled in three tables, with the corresponding GRADE tables.

The search strategy and references supporting the intervention and summary of evidence for all three tables are available in *Section 9* of this dossier.

7.1 Clopidogrel Versus Aspirin in Adults with Previous Myocardial Infarction, Stroke or Pad for the Secondary Prevention of Atherothrombotic Events

CLINICAL QUESTIONS
What is the efficacy and safety of clopidogrel compared to aspirin alone to prevent atherothrombotic events in adults when indicated for secondary prevention of myocardial infarction, stroke or peripheral arterial disease?

CONTEXT	Clopidogrel versus aspirin
Cardiovascular disease is a recognised cause of mortality and morbidity, which accounts up to17 million people dying of cardiovascular disease each year (*1*). Prophylaxis focuses on the modification of risk factors, but antiplatelet therapy improves the survival of patients with manifest cardiovascular disease. Aspirin has a protective effect in most patients at risk of cardiovascular events. The Antithrombotic Trialists' Collaboration showed the effects of aspirin in patients with acute myocardial infarction or ischemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischemia, peripheral arterial disease or atrial fibrillation (*2*). Thienopyridine derivatives inhibit platelet activation by a different mechanism and so may be more effective (*3*).	

INTERVENTION	Clopidogrel versus aspirin
Clopidogrel reduces the rate of myocardial infarction compared to aspirin in patients with atherosclerotic vascular disease. High quality evidence.	
Clopidogrel does not show differences in the rate of mortality for any cause or strokes compared to aspirin in patients with atherosclerotic vascular disease. Moderate quality evidence.	
Clopidogrel does not show differences in the risk of extracranial bleed or severe gastrointestinal hemorrhage compared to aspirin in patients with atherosclerotic vascular disease. Moderate quality evidence.	
Clopidogrel does not show differences in the risk of neutropenia or thrombocytopenia compared to aspirin in patients with atherosclerotic vascular disease. Moderate quality evidence.	
Clopidogrel increases the risk of skin rash compared to aspirin in patients with atherosclerotic vascular disease. High quality evidence.	

Summary of evidence	
Benefits	A Cochrane systematic review (10 RCTs) (3) and a health technology assessment (4 RTCs) (*4*) were found. The Cochrane review (date of search: December 2008) aimed to determine the effectiveness and safety of thienopyridine derivatives (ticlopidine and clopidogrel) versus aspirin for preventing serious vascular events (stroke, myocardial infarction (MI) or vascular death) in patients at high risk, and specifically in patients with a previous TIA or ischaemic stroke (*3*). The health technology assessment (date of search: September 2009) evaluated clopidogrel alone and modified release dipyridamole (MRD) alone or combination with aspirin compared with aspirin (*4*). Both reviews included the only RCT that compares directly clopidogrel and aspirin in the secondary prevention of cardiovascular events (5). The CAPRIE trial included 19,185 patients with atherosclerotic vascular disease manifested as a recent stroke, recent myocardial infarction, or symptomatic peripheral arterial disease. From these patients 6,431 had a recent ischaemic stroke likely to be of atherothrombotic origin, 6,302 patients had a recent myocardial infarction, and 6452 patients had atherosclerotic peripheral arterial disease. The study randomized patients to clopidogrel (75mg/day) or aspirin (325mg/day). The majority of patients were male (72%) with a mean age of 62.5 years, and a big proportion of patients with hypertension (74%) or diabetes mellitus (28%). The main outcome for this trial was a composite of ischaemic stroke, myocardial infarction, or vascular death. Secondary outcomes assessed were a composite of ischaemic stroke, myocardial infarction, leg amputation, or vascular death; vascular death; a composite of stroke, myocardial infarction or death from any cause; and death from any cause. After a mean follow-up of 1.9 years, clopidogrel showed an statistically significant difference compared to aspirin in the rate of the primary composite outcome of the CAPRIE trial (stroke, myocardial infarction, or vascular death) (1 RCT; 976/9599 events with clopidogrel vs 1063/9586 events with aspirin; Peto OR 0.91; 95%CI 0.83 to 0.99). When the outcomes were evaluated separately clopidogrel showed a significant reduction of the rate of myocardial infarction compared to aspirin (1 RCT; 276/9599 events with clopidogrel vs 505/9586 events with aspirin; Peto OR 0.80; 95%CI 0.68 to 0.94). However the results indicated no effect of clopidogrel over aspirin in the mortality for any cause (1 RCT; 560/9599 events with clopidogrel vs 571/9586 events with aspirin; Peto OR 0.98; 95%CI 0.87 to 1.10), or the rate of strokes (1 RCT; 464/9599 events with clopidogrel vs 505/9586 events with aspirin; Peto OR 0.91; 95%CI 0.80 to 1.04).
Risks	Results from the CAPRIE trial showed a similar rate of extracranial bleed between patients treated with clopidogrel or aspirin (1 RCT; 856/9599 events with clopidogrel vs 843/9586 events with aspirin; Peto OR 1.02; 95%CI 0.92 to 1.12). The rate of severe gastrointestinal hemorrhages also was similar between groups (1 RCT; 47/9599 events with clopidogrel vs 68/9586 events with aspirin; Peto OR 0.69; 95%CI 0.48 to 1.00). Clopidogrel and aspirin did not differ in the rate of other serious adverse events like neutropenia (1 RCT; 10/9599 events with clopidogrel vs 16/9586 events with aspirin; Peto OR 0.63; 95%CI 0.29 to 1.36) or thrombocytopenia (1 RCT; 25/9599 events with clopidogrel vs 25/9586 events with aspirin; Peto OR 1.00; 95%CI 0.57 to 1.74). The treatment with clopidogrel was associated with an increase in the rate of skin rash compared to aspirin (1 RCT; 578/9599 events with clopidogrel vs 442/9586 events with aspirin; Peto OR 1.32; 95%CI 1.17 to 1.50).
Comments/ Applicability	The authors of the Cochrane systematic review discussed that since clopidogrel it is not clearly more effective than aspirin, and it is substantially more expensive, it should generally only be used as monotherapy in patients who are genuinely intolerant of or allergic to aspirin (*3*).
Cost studies	A CRD assessed economic evaluation (*6*) synthesized the results of a study that used the data from the CAPRIE trial to examine the cost-effectiveness of clopidogrel versus aspirin as secondary prevention for patients who had experienced myocardial infarction or ischaemic stroke or were diagnosed with peripheral arterial disease (*7*). The study used a Markov model as the basis for the economic evaluation, with a time horizon of two years and a perspective of the third-party payers, and all the costs were expressed in euros. The summary benefit measures were estimated in terms of life-years (LYs). The authors used the Framingham database survival data to estimate that in a hypothetical cohort of 1,000 patients, the number of LYs saved, due to vascular deaths avoided, using clopidogrel compared with aspirin was 86.35. The incremental two-year cost of clopidogrel over aspirin was 1,241,440 euros. As results of this, the incremental cost per LY saved with clopidogrel over aspirin was 14,380 euros. The authors concluded that clopidogrel was a cost-effective alternative to aspirin as secondary prevention of cardiovascular or cerebrovascular events from the perspective of German third party payers.

Table 1. GRADE Evaluation of Clinical Outcomes (Patients with Atherosclerotic Vascular Disease - Assessment for All the Outcomes from Data in Reference *3*)

Number of studies (N))	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
1 (19,185)	Myocardial infarction	Clopidogrel ASA	4	0	0	0	0	High	
1 (19,185)	Mortality for any cause	Clopidogrel ASA	4	0	0	0	-1	Moderate	Imprecision in the results from CAPRIE resulting in wide confidence intervals
1 (19,185)	Stroke	Clopidogrel ASA	4	0	0	0	-1	Moderate	Imprecision in the results from CAPRIE resulting in wide confidence intervals
1 (19,185)	Extracranial bleed or severe gastrointestinal haemorrhage	Clopidogrel ASA	4	0	0	0	-1	Moderate	Imprecision in the results from CAPRIE resulting in wide confidence intervals
1 (19,185)	Neutropenia or thrombocytopenia	Clopidogrel ASA	4	0	0	0	-1	Moderate	Imprecision in the results from CAPRIE resulting in wide confidence intervals
1 (19,185)	Skin rash	Clopidogrel ASA	4	0	0	0	0	High	

Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion

7.2 Clopidogrel Plus Aspirin Versus Aspirin in Adults with an Acute Coronary Syndrome or for the Secondary Prevention of Atherothrombotic Events

CLINICAL QUESTIONS
What is the efficacy and safety of clopidogrel plus aspirin compared to aspirin alone to prevent atherothrombotic events in adults when indicated for secondary prevention of myocardial infarction, stroke or peripheral arterial disease? What is the efficacy and safety of clopidogrel plus aspirin compared to aspirin alone to prevent atherothrombotic events in adults with ST segment elevation or without ST segment elevation acute coronary syndrome?

CONTEXT	Clopidogrel plus aspirin versus aspirin
Cardiovascular disease is a recognised cause of mortality and morbidity, which accounts up to17 million people dying of cardiovascular disease each year (*1*). Prophylaxis focuses on the modification of risk factors, but antiplatelet therapy improves the survival of patients with manifest cardiovascular disease. Aspirin has a protective effect in most patients at risk of cardiovascular events. The Antithrombotic Trialists' Collaboration showed the effects of aspirin in patients with acute myocardial infarction or ischemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischemia, peripheral arterial disease or atrial fibrillation (*2*). Adding a second antiplatelet drug to aspirin may produce additional benefit for those at high risk and those with established cardiovascular disease. The combination of clopidogrel and aspirin could be a strategy to reduce cardiovascular disease (*3*).	

INTERVENTION	Clopidogrel plus aspirin versus aspirin
Clopidogrel plus aspirin compared to aspirin in patients with established cardiovascular disease Clopidogrel plus aspirin does not show differences in the rate of major coronary events or the risk of major bleeding compared to aspirin alone in patients with established cardiovascular disease. Moderate quality evidence.	
Clopidogrel plus aspirin compared to aspirin in patients with non-ST-segment elevation acute coronary syndrome Clopidogrel plus aspirin reduces the rate of major coronary events but increases the risk of major bleeding compared to aspirin alone in patients with non-ST-segment elevation acute coronary syndrome. High quality evidence.	
Clopidogrel plus aspirin compared to aspirin in patients with a ST-elevation myocardial infarction Clopidogrel plus aspirin reduces the rate of major coronary events and do not show differences in the rate of major bleeding compared to aspirin alone in patients with a ST-elevation myocardial infarction. Moderate quality evidence.	

Summary of evidence	
Benefits	A Cochrane systematic review (2 RCTs) was found (*3*). The review aimed to assess the benefit and harm of adding clopidogrel to standard long-term aspirin therapy for preventing cardiovascular events in people at high risk of cardiovascular disease and those with established cardiovascular disease. The eligibility criteria were restricted to RCTs comparing aspirin plus clopidogrel with aspirin with a follow-up higher than 30 days. The review included the only randomized trial that assessed the effects of clopidogrel in addition to aspirin in patients with an acute coronary syndrome (ACS) without ST-segment elevation (*4*). The studies in patients with ACS and an elevation of the ST-segment are limited at the short term (a maximum of 30 days of follow-up) and were considered in an additional systematic review (*5*). Ultimately, the potential benefit of adding clopidogrel to aspirin over aspirin alone was assessed in the following trials: CHARISMA (*6*): the trial randomized 15,603 people at high risk for a cardiovascular event either to receive clopidogrel (75mg/day) plus aspirin (75 to 162mg/day) or placebo plus low-dose aspirin. The trial included mostly male patients (70%) with a median age of 64 years, which had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebro-vascular disease, or documented symptomatic peripheral arterial disease. The primary outcome was a composite of the first occurrence of myocardial infarction, stroke, or death from cardiovascular causes, after a median of 28 months of follow-up. The trial also assessed a composite outcome of first occurrence of the primary endpoint, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure. The main safety outcome was severe bleeding according a standardized definition (GUSTO definition). CURE (*4*): the trial randomized a total of 12,562 people with a non-ST-segment elevation ACS to receive clopidogrel (loading dose of 300mg followed by 75mg/day) plus aspirin (75 to 325mg/day) or placebo plus aspirin. The trial included mostly male patients (72%) with a median age of 64 years. The primary outcome was a composite of death from cardiovascular causes, non-fatal acute myocardial infarction, or stroke. Additionally, the trial also assessed a combined endpoint of the primary endpoint and refractory ischemia. The main safety outcome was life threatening, severe or minor bleeding. COMMIT (*7*): the trial randomized a total of 45,852 patients hospitalized within 24 hours of suspected ST-segment elevation myocardial infarction to receive clopidogrel (75mg/day) plus aspirin (162mg/day) or placebo plus aspirin. The trial included mostly male patients (72%) with a median age of 61 years that continued the treatment until hospital discharge or up to 4 weeks. The trial defined two primary outcomes: i) a composite of death, re-infarction, or stroke and, ii) death from any cause. The trial assessed safety of clopidogrel through the rates of hemorrhagic stroke and major non-cerebral bleeding. CLARITY (*8*): randomized 3,491 patients that were admitted to the hospital within 12 hours after the onset of an ST-elevation myocardial infarction to receive clopidogrel (loading dose of 300mg followed by 75mg/day) and aspirin (150 to 325mg on the first day followed by 75 to 162mg/day) or placebo plus aspirin. Additionally all patients were to be treated with a fibrinolytic and were scheduled to undergo angiography 48 to 192 hours after the start of study medication. Patients in this trial had an average age of 57 years and 80% were men. The primary outcome was a composite of the occurrence of an occluded infarct-related artery on angiography, death, or re-infarction before angiography. The safety outcome was the rate of major bleeding. **Benefits of clopidogrel plus aspirin compared to aspirin alone in patients with established cardiovascular disease** A Cochrane systematic review (*3*), based in the results from the CHARISMA trial (6), showed that in patients at high cardiovascular risk defined either in terms of pre-existing cardiovascular diseases or risk factors, the combination of clopidogrel and aspirin did not show an statistically significant difference in the rate of cardiovascular events compared to aspirin alone, although the rate of cardiovascular events were lower in the dual antiplatelet group than in the aspirin group (1 RCT; 490/7802 events with dual antiplatelet vs 530/7801 events with aspirin; OR 0.92; 95%CI 0.81 to 1.04). The review estimated that the number needed to treat to avoid 1 cardiovascular event

continues

Summary of evidence	
Benefits *(cont.)*	was 194, and that 5 cardiovascular events would be avoided for every 1000 people treated for an average of 28 months with clopidogrel plus aspirin compared to those treated with aspirin alone. **Benefits of clopidogrel plus aspirin compared to aspirin alone in patients with a non-ST-segment elevation acute coronary syndrome** The Cochrane systematic review (*3*), based in the results from the CURE trial (*4*), showed that in patients with acute non-ST segment coronary syndromes, the combination of clopidogrel and aspirin reduces the rate of cardiovascular events compared with aspirin alone (1 RCT; 936/6259 events with dual antiplatelet vs 1088/6303 events with aspirin; OR 0.84; 95%CI 0.77 to 0.93). The number needed to treat to avoid 1 cardiovascular event was 43, and that 23 cardiovascular events would be avoided for every 1000 people treated for an average of 9 months with clopidogrel plus aspirin compared to those treated with aspirin alone. **Benefits of clopidogrel plus aspirin compared to aspirin alone in patients with a ST-elevation myocardial infarction** The data showed in a systematic review (*5*) allowed the pooled analysis for the rate of major coronary events and mortality from the two trials that compared dual antiplatelet therapy with aspirin in patients with a ST-elevation myocardial infarction (COMMIT (7) and CLARITY (*8*)). For those patients the combination of clopidogrel and aspirin reduces the rate of major coronary events compared to aspirin alone (1 RCT; 2280/24713 events with dual antiplatelet vs 2500/24630 events with aspirin; OR 0.90; 95%CI 0.85 to 0.96; figure 1). Both treatments did not show an statistically significant difference in the rate of all cause mortality, but the rate of all cause mortality was lower between the patients treated with clopidogrel and aspirin (1 RCT; 1798/24713 events with dual antiplatelet vs 1948/24630 events with aspirin; OR 0.83; 95%CI 0.62 to 1.11; figure 2). The review did not report data of the absolute benefit of the combined therapy, but an estimation of these results shows that 9 major coronary events would be avoided for every 1000 people treated with clopidogrel plus aspirin compared to those treated with aspirin alone.
Risks	**Risk of major bleeding with clopidogrel plus aspirin compared to aspirin alone in patients with established cardiovascular disease** The results from the CHARISMA trial (*6*) included in the Cochrane systematic review (*3*), showed a non-statistically significant increase in the risk of major bleeding in patients treated with the combination of clopidogrel and aspirin compared with aspirin (1 RCT; 130/7802 events with dual antiplatelet vs 104/7801 events with aspirin; OR 1.25; 95%CI 0.97 to 1.63). The review estimated that the number needed to treat to cause 1 major bleed was 300, and that 3 major bleeds would be caused for every 1000 people treated for an average of 28 months with clopidogrel plus aspirin compared to those treated with aspirin alone. **Risk of major bleeding with clopidogrel plus aspirin compared to aspirin alone in patients with a non-ST-segment elevation acute coronary syndrome** The Cochrane systematic review (*3*), based in the results from the CURE trial (*4*), showed that in patients with acute non-ST segment coronary syndromes, the combination of clopidogrel and aspirin increased the risk of major bleeding compared with aspirin alone (1 RCT; 231/6259 events with dual antiplatelet vs 169/6303 events with aspirin; OR 1.39; 95%CI 1.14 to 1.70). The number needed to treat to cause 1 major bleed was 99, and that 10 major bleeds would be caused for every 1000 people treated for an average of 9 months with clopidogrel plus aspirin compared to those treated with aspirin alone. **Risk of major bleeding with clopidogrel plus aspirin compared to aspirin alone in patients with a ST-elevation myocardial infarction** The data provided in a systematic review (*5*) allowed the pooled analysis for the rate of major bleeding from the COMMIT (7) and CLARITY (*8*) trials. In patients with a ST-elevation myocardial infarction the combination of clopidogrel and aspirin was not associated with a significant increase of major bleeding compared to aspirin alone (1 RCT; 167/24713 events with dual antiplatelet vs 155/24630 events with aspirin; OR 1.07; 95%CI 0.86 to 1.34; figure 3).

Summary of evidence	
Comments/ Applicability	The authors of the Cochrane review (*3*) concluded that the available evidence shows that in patients with cardiovascular disease the addition of clopidogrel to long-term administration of aspirin has a small and non-significant beneficial effect that contrasts with an increase in the risk of bleeding. The authors affirm that even a small benefit may be desirable in a prevalent problem as such as atherothrombosis.
	This small effect of dual antiplatelet compared to aspirin with established cardiovascular disease should be interpreted in the light of two potential limitations for the applicability of the results. First, the authors of the review decided to report data exclusively data on all cardiovascular events and major bleeding due to the suspicion of selective reporting bias of several secondary outcomes in the published trials data. On the other hand the CHARISMA trial (*6*) included people with a wide range of conditions precluding the identification of which kind of patient could benefit more of the combination of clopidogrel and aspirin. In that sense, the results of a series of ongoing trials identified in the Cochrane review should clarify the risk-benefit of the combined therapy in specific subgroup populations.
	Regarding patients with an acute coronary syndrome with a non-ST-segment elevation the two assessed systematic reviews coincide in conclude that the benefits of clopidogrel combined with aspirin outweighing major bleeding events (*3,5*). It should be noted, however, that it remains unclear if the beneficial effect is largely due to early post-acute event combination therapy and the benefits at the long term are unknown.
	The studies in patients with a ST-elevation myocardial infarction (*7,8*) assessed the effects of the combination of clopidogrel and aspirin at the short term and could underestimate the risk of bleeding.
Cost studies	The search did not retrieved relevant economic evaluations assessing the cost-effectiveness of combined antiplatelet therapy with clopidogrel plus aspirin compared with aspirin alone in patients with established cardiovascular disease, or patients with a ST-elevation myocardial infarction. **Clopidogrel plus aspirin compared to aspirin alone in patients with a non-ST-segment elevation acute coronary syndrome** A CRD assessed economic evaluation (*9*) synthesized a health technology assessment (*10*) that performed a cost-utility analysis with the perspective of the UK National Health System. The study used a hypothetical cohort of patients with non-ST-segment elevation ACS using clinical data from the CURE trial (*4*), with a 2001/02 price base. The study constructed a probabilistic decision model with a lifetime horizon (40 years) in two parts (a short-term element standard decision tree, and a long-term model). The long term model was modeled using a Markov model. The summary measure used was the quality-adjusted life-years (QALYs). The results showed that the lifetime QALYs was 8.2795 with clopidogrel and 8.2022 with the standard therapy, and the expected lifetime costs per patient were £12,695 with clopidogrel and £12,225 with the standard treatment. The incremental cost per QALY gained with clopidogrel over usual treatment was £6,078. The authors concluded that the combination of clopidogrel and aspirin was a cost-effective treatment for patients with non-ST-segment elevation acute coronary syndrome, and that shorter treatment durations for clopidogrel might be more cost-effective in patients at low risk.

Figures: Pooled analysis for major cardiovascular events, all-cause mortality and major bleeding in patients with a ST-elevation myocardial infarction treated with clopidogrel plus aspirin compared to aspirin alone from the COMMIT (*7*) and CLARITY (*8*) trials (data obtained from the Bowry 2008 systematic review (*5*))

Figure 1.- Major Cardiovascular Events

	Clopi+ASA		ASA			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CLARITY	159	1752	190	1739	7.2%	0.81 [0.65, 1.02]	
COMMIT	2121	22961	2310	22891	92.8%	0.91 [0.85, 0.96]	
Total (95% CI)		**24713**		**24630**	**100.0%**	**0.90 [0.85, 0.96]**	
Total events	2280		2500				

Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 3.47 (P = 0.0005)

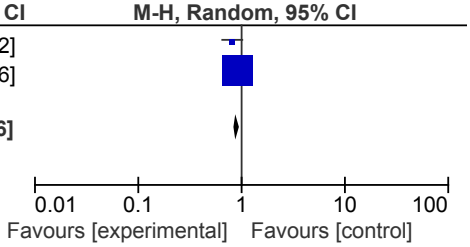

Figure 2.- All-Cause Mortality

	Clopi+ASA		ASA			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CLARITY	72	1752	103	1739	37.6%	0.68 [0.50, 0.93]	
COMMIT	1726	22961	1845	22891	62.4%	0.93 [0.87, 0.99]	
Total (95% CI)		**24713**		**24630**	**100.0%**	**0.83 [0.62, 1.11]**	
Total events	1798		1948				

Heterogeneity: Tau² = 0.03; Chi² = 3.67, df = 1 (P = 0.06); I² = 73%
Test for overall effect: Z = 1.28 (P = 0.20)

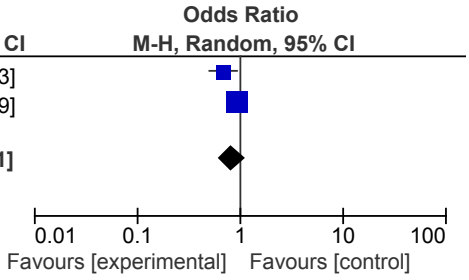

Figure 3.- Major Bleeding

	Clopi+ASA		ASA			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CLARITY	33	1752	30	1739	19.4%	1.09 [0.66, 1.80]	
COMMIT	134	22961	125	22891	80.6%	1.07 [0.84, 1.37]	
Total (95% CI)		**24713**		**24630**	**100.0%**	**1.07 [0.86, 1.34]**	
Total events	167		155				

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)

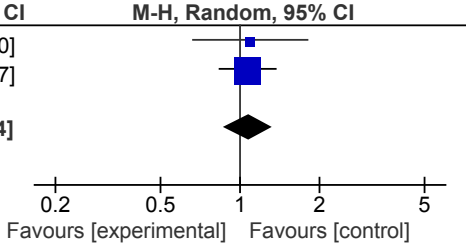

Table 1. GRADE Evaluation of Clinical Outcomes (Patients with Atherosclerotic Vascular Disease - Assessment for all the Outcomes from Data in Reference 3)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
1 (15.603)	Cardio-vascular events	Clopidogrel + ASA ASA	4	0	0	0	-1	Moderate	Imprecision in the results from CHARISMA trial that failed to demonstrate or exclude an effect (wide confidence intervals)
1 (15.603)	Major bleeding	Clopidogrel + ASA ASA	4	0	0	0	-1	Moderate	Imprecision in the results from CHARISMA trial that failed to demonstrate or exclude an effect (wide confidence intervals)
Patients with a non-ST-segment elevation acute coronary syndrome (assessment for all the outcomes from data in reference 3)									
1 (12.562)	Cardio-vascular events	Clopidogrel + ASA ASA	4	0	0	0	0	High	
1 (12.562)	Major bleeding	Clopidogrel + ASA ASA	4	0	0	0	0	High	
Patients with a ST-elevation myocardial infarction (assessment for all the outcomes from data in reference 5)									
2 (49.343)	Major coro-nary events	Clopidogrel + ASA ASA	4	0	0	0	0	High	
2 (49.343)	All cause mortality	Clopidogrel + ASA ASA	4	0	-1	0	0	Moderate	High heterogeneity (I^2 73%)
2 (49.343)	Major bleeding	Clopidogrel + ASA ASA	4	0	0	0	0	High	

Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion

7.3 Clopidogrel Plus Aspirin Versus Warfarin in Adults with Atrial Fibrillation

CLINICAL QUESTION
What is the efficacy and safety of clopidogrel plus aspirin compared to warfarin to prevent atherothrombotic and thromboembolic events in adults with atrial fibrillation?

CONTEXT	Clopidogrel plus aspirin versus warfarin
Atrial fibrillation is a common cardiac arrhythmia that put patients at an increased risk of stroke mediated by embolism of stasis-precipitated thrombi originating in the left atrial appendage (*1*). It affects about 0.7% of the general population and its prevalence increases with age. The identification of additional risk factors in people with atrial fibrillation is important for selecting the appropriate prophylactic therapy. Age, hypertension, prior stroke, diabetes, and female gender are independently predictive of stroke in atrial fibrillation patients. Antiplatelet therapy reduces stroke and other major vascular events for those with non-valvular atrial fibrillation compared with no antithrombotic treatment, but the effect of treatments such as aspirin is modest (about 25%) (*1*). Adjusted-dose warfarin offers larger reductions in stroke for these patients when the treatment can be prescribed safely, and maximum protection is reached by maintaining the international normalized ratio (INR) between 2.0 and 3.0. Adjusted-dose warfarin for atrial fibrillation patients at high risk for stroke is recommended in many guidelines, while aspirin is recommended for those patients at low risk or for those who cannot safely receive adjusted-dose warfarin (*1*). The goal of effective, simple and safe alternative to anticoagulation has aimed researchers to assess the benefits of other antiplatelet treatments (*2*).	

INTERVENTION	Clopidogrel plus aspirin versus warfarin
VKA therapy reduces the rate of stroke, ischemic stroke, and non-CNS embolism compared to clopidogrel and aspirin in patients with atrial fibrillation. High quality evidence.	
Clopidogrel plus aspirin does not show differences in the rate of all cause mortality, myocardial infarction, vascular death or intracranial hemorrhages compared to VKA therapy in patients with atrial fibrillation. Moderate quality evidence.	
Clopidogrel plus aspirin does not show differences in the rate of major extracranial bleeding compared to VKA therapy in patients with atrial fibrillation. Moderate quality evidence.	

Summary of evidence	
Benefits	A Cochrane systematic review (8 RCTs) was found (*1*). The review aimed to assess the effects of long-term treatment with oral anticoagulants compared with antiplatelet therapy in the rate of major vascular events in patients with non-valvular atrial fibrillation, without a history of stroke or transient ischemic attack. The review included the only trial that has compared the combination of clopidogrel and aspirin with a vitamin K antagonist (VKA) therapy: The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) W trial (2). In this non-inferiority trial 6,706 patients with atrial fibrillation confirmed by electrocardiogram were allocated randomly to receive oral anticoagulation therapy or a combination of clopidogrel (75mg/day) plus aspirin (75 to 100mg/day). Patients randomized to oral anticoagulation received the vitamin K antagonist in use in their country and were monitored to keep the international normalized ratio (INR) between 2 and 3. Patients had a mean age of 70.2 years, 15% had a history of previous stroke or transient ischemic attack, and 77% received VKA therapy before randomization. The primary outcome in this study was a composite of stroke, systemic embolism, myocardial infarction, or vascular death. The trial registered the number of minor, major and severe bleedings as the safety outcome.

continues

Summary of evidence	
Benefits *(cont.)*	It is noteworthy that the trial was stopped early because the superiority of VKA therapy in the analysis for the primary outcome (1 RCT; annual risk 5,60% with dual antiplatelet vs annual risk 3.93% VKA therapy; RR 1.44; 95%CI 1.18 to 1.76) and the absence of a difference in the risk of major bleeding. In the ACTIVE W VKA therapy resulted in a statistically significant reduction of the risk of stroke compared with the combination of clopidogrel and aspirin (1 RCT; 106/3335 events with dual antiplatelet vs 64/3371 events with VKA therapy; Peto OR 0.60; 95%CI 0.44 to 0.81). The difference between the compared treatments was more marked in the rate of ischemic strokes (1 RCT; 94/3335 events with dual antiplatelet vs 43/3371 events with VKA therapy; Peto OR 0.46; 95%CI 0.33 to 0.65). The rate of systemic (non-CNS) embolisms was also lower between patients that received VKA therapy compared to the combination of clopidogrel and aspirin (1 RCT; 18/3335 events with dual antiplatelet vs 5/3371 events with VKA therapy; Peto OR 0.32; 95%CI 0.14 to 0.72). On the other hand, the treatments did not show differences in the rate of myocardial infarction (1 RCT; 36/3335 events with dual antiplatelet vs 23/3371 events with VKA therapy; Peto OR 0.63; 95%CI 0.38 to 1.06), intracranial hemorrhages (1 RCT; 11/3335 events with dual antiplatelet vs 21/3371 events with VKA therapy; Peto OR 1.85; 95%CI 0.93 to 3.71), all cause mortality (1 RCT; 160/3335 events with dual antiplatelet vs 159/3371 events with VKA therapy; Peto OR 0.98; 95%CI 0.78 to 1.23) or vascular death (1 RCT; 120/3335 events with dual antiplatelet vs 108/3371 events with VKA therapy; Peto OR 0.89; 95%CI 0.68 to 1.15).
Risks	The results from the ACTIVE W trial (2) included in the Cochrane systematic review (*1*), showed a similar risk of major extracranial bleeding in patients treated with the combination of clopidogrel and aspirin compared with VKA therapy (1 RCT; 89/3335 events with dual antiplatelet vs 72/3371 events with VKA therapy; Peto OR 0.80; 95%CI 0.58 to 1.09).
Comments/ Applicability	The assessed Cochrane review assessed the effects of antiplatelet therapy compared to oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke (*1*). When the results for major extracranial haemorrhages were pooled the ACTIVE W was the only trial did not show differences between the combination of clopidogrel and aspirin and VKA therapy. The remaining trials showed that major extracranial haemorrhages were more common in the oral anticoagulant group.
	The high rate of patients that received VKA therapy before randomization in the ACTIVE W trial (*2*) could entail a problem of generalizability of its findings to patients who are newly in receive VKA therapy. Despite this, a prespecified subgroup analysis of the trial results did not show differences in the effect of VKA therapy on the primary outcome in patients who were and were not receiving VKA therapy at study entry.
	Having into account that guidelines recommend adjusted-dose warfarin for atrial fibrillation patients at high risk for stroke and aspirin for those deemed at low risk or for those who cannot safely receive adjusted-dose warfarin (*1*), it becomes necessary to use some of the stroke risk stratification schemes that have been validated for atrial fibrillation patients. The threshold of benefit that would warrant anticoagulation remains controversial and depends on patient preferences and availability of optimal anticoagulation monitoring (*1*). For patients with a contraindication to anticoagulation or for those that cannot guarantee an accurate anticoagulation monitoring it remains necessary to identify antithrombotic agents that are safer and easier to use than adjusted-dose warfarin.
Cost studies	The search did not retrieved relevant economic evaluations assessing the cost-effectiveness of combined antiplatelet therapy with clopidogrel plus aspirin compared with VKA therapy in patients with atrial fibrillation.

Table 1. GRADE Evaluation of Clinical Outcomes (Patients with Established Cardiovascular Disease - Assessment for all the Outcomes from Data in Reference 1)

Number of studies (N))	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
1 (6.706)	Mortality	Clopidogrel + ASA Warfarin	4	0	0	0	-1	Moderate	Imprecision in the results from ACTIVE W trial that failed to demonstrate or exclude an effect (wide confidence intervals)
1 (6.706)	Stroke	Clopidogrel + ASA Warfarin	4	0	0	0	0	High	
1 (6.706)	Myocardial infarction	Clopidogrel + ASA Warfarin	4	0	0	0	-1	Moderate	Imprecision in the results from ACTIVE W trial that failed to demonstrate or exclude an effect (wide confidence intervals)
1 (6.706)	Major extracranial bleeding	Clopidogrel + ASA Warfarin	4	0	0	0	-1	Moderate	Imprecision in the results from ACTIVE W trial that failed to demonstrate or exclude an effect (wide confidence intervals)
1 (6.706)	Intracranial haemor-rhages	Clopidogrel + ASA Warfarin	4	0	0	0	-1	Moderate	Imprecision in the results from ACTIVE W trial that failed to demonstrate or exclude an effect (wide confidence intervals)
1 (6.706)	Systemic (non-CNS) embolisms	Clopidogrel + ASA Warfarin	4	0	0	0	0	High	

Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion

8. Special Considerations and Additional Comments (*11-20*)

8.1 Regulatory Status of the Product in National Regulatory Authorities (NRAs)

The following table reflects the regulatory status of the product (innovator and generic – if applicable) in the 7 PAHO Region Reference NRAs (Argentina, Brazil, Canada, Colombia, Cuba, Mexico and United States) and the European Medicine Agency.

NRA	Status	
	Innovator	Generic
Argentina (ANMAT)	x	x
Brazil (ANVISA)	x	x
Canada (Health Canada)	x	x
Colombia (INVIMA)	x	x
Cuba (CECMED)	x	x
Mexico (COFEPRIS)	x	x
USA (FDA)	x	x
Europe (EMA)	x	x

8.2 PAHO Member State Prices

Through ECONMED (an electronic listserv for public officials from the health sector), PAHO requested the price paid for procurement of clopidogrel from Member States who utilize this products in their National Public Health Programs. Unfortunately, no data has been provided to PAHO by countries in Latin America and the Caribbean. PAHO will increase efforts to obtain some prices from Member States and will distribute the information when the committee convenes in Washington, D.C.

8.3 Results of PAHO Expression of Interest

For a medicine to be eligible for inclusion in the PAHO Strategic Fund medicine list, it must have supporting evidence of safety, efficacy, and clinical effectiveness. Additionally the product must satisfy one of the following criteria as related to the pharmaceutical market:

1. The acquisition of the medicines is subject to particular challenges related to product procurement, pricing, patent status, forecasting of future needs, and exclusivity contracts between pharmaceutical companies that restrict marketing in specific geographical areas.
2. Leveraging economies of scale (increases in the volume of medicine procured) can result in lower costs.

PAHO has established this criteria to ensure the inclusion of the product in the Strategic Fund will provide value added to Member States who procure this product through PAHO.

To evaluate these pharmaceutical market factors, the Procurement (PRO) Unit of PAHO conducted an Expression of Interest (EoI) to gather information related to the product. PRO contacted 19 suppliers, which are included in the PAHO approved supplier list, and asked for product data (i.e. available presentations, manufacturing origin & capacity, potential restrictions, prices, and available technical documents).

Limited response was obtained from the contacted suppliers; however, PRO believes clopidogrel, does meet the pharmaceutical market criteria. Nonetheless, significant challenges are present and the following are key recommendations:

- Consolidate regional demand to leverage the benefits of economies of scale. If PAHO is able to obtain sufficient demand perform an international tender and establish Long Term Agreements with suppliers.
- Increase number of PAHO approved suppliers offering this product in order to ensure availability and create a more competitive market.

8.4 Potential Value Added for Procurement of the Medicine through the Strategic Fund

The current version of the Strategic Fund medicine list, published in April of 2013, does not include any platelet aggregation inhibitors. Aspirin, a low cost antiplatelet therapy utilized to prevent atherothrombotic events, is not included in the Strategic Fund as most countries have adequate access at affordable prices and procuring through PAHO would not provide significant value added. If the presented evidence demonstrates adequate safety, efficacy, and clinical effectiveness, PAHO believes the inclusion of this product will improve Member States access to an effective and safe medicine that can be used to reduce the burden of cardiovascular disease.

In comparison to aspirin, clopidogrel is significantly more expensive. For example, 2011 reference prices indicate Clopidogrel 75 mg (US$ 0.2177 per unit) cost 15 times the cost of Aspirin 75 mg (US$ 0.0143 per unit) and 80 times the cost of Aspirin 300 mg (US$ 0.0026 per unit). If included in the Strategic Fund List, PAHO would aim to consolidate regional demand to lower the costs of the product, thus easing the financial burden on Member States.

9. Search Strategy and References Supporting Intervention and Summary of Evidence

The interventions and summary of evidences presented in the three separate tables above in *Section VII.a-c* where all conducted with the same search strategy; however, each table yielded different results (selection criteria and the search strategy results). These differences are identified below is the table titled *Differences in the Selection Criteria and Search Results for each Clinical Question*. Additionally, the corresponding references for each clinical question are presented.

9.1 Inclusion Criteria

The aim of this evidence summary is to gather information from a systematic review about the benefits and risk of a drug in a specific health problem. For this reason we include in the summary the results from a rigorous systematic review, prioritizing Cochrane reviews. When a Cochrane review is not available or it is not suitable to respond the scope of the clinical question, we consider the inclusion of a systematic review that at least: i) includes a clearly defined inclusion criteria; ii) reports a recent search in at least two databases; and iii) reports any efforts from authors to assess the risk of bias from the included studies.

These criteria are the minimum requirements established by the Centre for Reviews and Dissemination to include a systematic review in the Database of Abstracts of Reviews of Effects (DARE; www.crd.york.ac.uk/

crdweb/AboutPage.asp). For the specific purposes of the "Cost studies" section we include the results from an economic evaluation, that is; a comparison of two or more interventions or care alternatives (including cost-benefit analyses, cost-utility analyses, and cost-effectiveness analyses).

9.2 Search for Studies

The inclusion criteria described above determines the search for the studies planned. We design specific search algorithms to search the AHRQ Effective Health Care Program and The Cochrane Library as the main source to retrieve high quality systematic reviews. Each search in these two resources is complemented with a search in MEDLINE (accessed through PubMed) with the purpose of check any additional or more recent systematic review. The search is performed without any limitation, with the exception of PubMed in which we limit the search to the validated subset of systematic reviews (systematic[sb]). As we included only economic evaluations in the "Cost studies" section we limit the search to the NHS EED Database. In those cases that the NHS EED Database does not provide relevant results, we perform a specific search in MEDLINE, limiting the search algorithm designed to retrieve systematic review with the term cost*[tiab]. The search to develop the present clinical question was performed in May 2013, with the search strategies detailed in the below is the table titled Differences in the Selection Criteria and Search Results for each Clinical Question.

9.3 Rating the Quality of the Evidence

Each evidence summary provides a rating of the quality of evidence following the GRADE guidance. GRADE specifies four categories (high, moderate, low, and very low) that are applied to the body of evidence that supports each assessed outcome. In the context of a synthesis of the evidence the quality of evidence reflects the confidence that the estimates of the effect are correct. For each clinical question one experienced researcher collects in a table the number of studies and patients included in these studies that set the body of evidence for each specific outcome discussed in the "Benefits" and "Risks" sections. The quality of evidence is then rated for each specific outcome and a final category is provided, commenting the main limitations that compromise the quality of evidence. All the information collected in the table, and the details required to the rating of the quality of evidence are obtained from the assessed systematic review used to develop the evidence summary.

9.4 Selection Criteria

One experienced researcher screens the results from the search applying the inclusion criteria commented above. If a Cochrane review is identified, it is selected to develop the evidence summary. When a Cochrane review is not suitable to respond to the scope of the formulated clinical question, the references from MEDLINE are screened.

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
Clopidogrel versus aspirin in adults with previous myocardial infarction, stroke or PAD for the secondary prevention of atherothrombotic events	For the purposes of this clinical question, a Cochrane review was identified from the records retrieved from the Cochrane Database of Systematic Reviews (3), and a health technology assessment from the 63 record retrieved in MEDLINE complemented the data to develop the evidence summary.	■ **Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ clopidogrel 0 hits ■ **Cochrane Database of Systematic Reviews : Issue 4 of 12, April 2013** (clopidogrel AND aspirin):ti,ab,kw 689 hits ■ **MEDLINE (accessed via PubMed)** clopidogrel[ti] AND (aspirin[tiab] OR ASA[tiab]) AND systematic[sb] 63 hits ■ **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (Clopidogrel):TI IN NHSEED 44 hits
Clopidogrel plus aspirin versus aspirin in adults with an acute coronary syndrome or for the secondary prevention of atherothrombotic events	For the purposes of this clinical question, a Cochrane review was identified from the records retrieved from the Cochrane Database of Systematic Reviews (3). As the review did not considered trials at short term, any trial including patients with ACS and an elevation of the ST-segment were missed. The screening of the 63 records retrieved from MEDLINE allowed the identification of an additional systematic review (5) that included two trials in this setting (7,8).	■ **Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ clopidogrel 0 hits ■ **Cochrane Database of Systematic Reviews : Issue 4 of 12, April 2013** (clopidogrel AND aspirin):ti,ab,kw 689 hits ■ **MEDLINE (accessed via PubMed)** clopidogrel[ti] AND (aspirin[tiab] OR ASA[tiab]) AND systematic[sb] 63 hits ■ **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (Clopidogrel):TI IN NHSEED 44 hits

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
Clopidogrel plus aspirin versus warfarin in adults with atrial fibrillation	For the purposes of this clinical question, a Cochrane review was identified from the records retrieved from the Cochrane Database of Systematic Reviews (1).	■ **Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ clopidogrel 0 hits ■ **Cochrane Database of Systematic Reviews : Issue 4 of 12, April 2013** (clopidogrel AND warfarin AND atrial):ti,ab,kw 12 hits ■ **MEDLINE (accessed via PubMed)** clopidogrel[ti] AND warfarin[tiab] AND systematic[sb] 5 hits clopidogrel[ti] AND warfarin[tiab] AND cost*[tiab] 2 hits ■ **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (clopidogrel) AND (atrial fibrillation) IN NHSEED 0 hits (clopidogrel) AND (warfarin) IN NHSEED 5 hits

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10. Additional References

The following references are those cited in Section 2 (Public Health Relevance), Section 4 (Medicine Characteristics and Pharmacological Information) and Section 8 (Special Considerations and Additional Comments). References supporting the intervention and summary of evidence are available in Sections 9.5 - 9.7.

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Annex 3

Review of the Available Evidence of Lisinopril Tablet (5 & 20 mg) for Potential Inclusion in the Pan American Health Organization Strategic Fund Medicine List

Annex 3: Table of Contents

1. Introduction to the PAHO Strategic Fund

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (Strategic Fund) was created by the Director of the Pan American Health Organization (PAHO) at the request of Member States of the Organization, in September 1998 during the 35th session of the Pan American Sanitary Conference.

The Strategic Fund is a regional mechanism which aims to strengthen the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe and effective supplies at affordable prices obtained by leveraging the advantages of economies of scale.

To accomplish this objective the Strategic Fund publishes a list of medicines available for procurement in name of the Organization's Member States. The list utilizes as a foundation the World Health Organization (WHO) Essential Medicines List (EML); however, recently there has been a significant increase in Member State requests to procure products not included in the WHO EML.

In order to meet the needs of PAHO Member States the PAHO Director has created an external Expert Committee to review requests for inclusion of medicines not included in the WHO EML. This Expert Committee will allow PAHO to implement a decision making mechanism in agreement with concepts of quality, efficacy, safety and when available, information related to the value they provide in relation to their cost.

The committee will work exclusively on requests to update the SF medicine list, which will enable PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this EC should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

2. Public Health Relevance (*1-3*)

2.1 NCDs in the Region of the Americas

Over the last decades, noncommunicable diseases (NCDs) have become the leading cause of morbidity and mortality across the globe while imposing a growing threat to international development goals and economic growth as well as contributing to dramatic rises in health care expenditures.

The main NCDs principally include cardiovascular disease, cancer, diabetes and respiratory diseases and are accompanied by various common risk factors rising at a rapid pace. In the Americas region, NCDs are responsible for 3 out of every 4 deaths with cardiovascular diseases and cancer as the leading causes responsible respectively for 1.9 million and 1.2 million deaths each year. More than one third of these deaths are premature and occur in people under the age of 70 years old therefore leading to serious repercussions on social and economic development.

Noncommunicable diseases not only slow down development but also place a heavy financial burden on patients, healthcare and governments. The costs to overall health systems are expect to rise as governments are expected to increase funding to prevent and treat these diseases. Confronting the rising costs constitutes a real challenge in low and middle income countries of the Americas where economic growth is often compromised and healthcare systems have to manage access and equity issues. Patients are facing similar issues, as in many countries healthcare costs are paid out-of-pocket and the impact of NCDs on household budgets and healthcare expenditures can often lead to catastrophic spending and impoverishment.

In some countries of the region, out-of-pocket expenditures account for 78% of spending on medicines. Cardiovascular diseases constitute an important family expenditure on healthcare and can become an enormous economic and social burden in low-and-middle income countries. For example, patients suffering from more than two chronic diseases and taking more than two medicines for these conditions account for 10% of all patients in some countries. Health expenditures for this population can reach 50% of the overall health expenditure. Hence, in Latin America, out-of-pocket expenses related to NCDs and health expenditures accounting for chronic diseases represent a critical health care and financial issue.

In response to the NCD situation in the Americas, the 28th Pan American Sanitary Conference in September 2012, adopted the Regional Strategy for the Prevention and Control of Noncommunicable Diseases (Resolution CSP28.R13 aims to:

> "reorient and strengthen health systems to improve coverage, access to and quality of care provided to the people with NCDs or their risk factors, based on primary health care"

This process is linked with the WHO voluntary global NCD targets for 2025, which aims to achieve the following:

- 25% relative reduction of premature mortality due to noncommunicable diseases
- 80% coverage of essential NCD medicines and technologies
- 50% coverage of drug therapy and counseling.

As a critical component of PAHO's response to these issues, the Strategic Fund is increasing support and assistance to Member States by amplifying the list of NCD medicines for countries to procure. Thus, increasing access to quality drugs and helping ease the increasing financial burden, specifically for new or high cost medicines.

The Strategic Fund has initiated a process to review the available evidence regarding the efficacy, safety and cost-effectiveness of NCD medicines, particularly for cardiovascular diseases and cancer. The following document presents the status of the medicine, basic pharmacological information, the evidence comparing the requested medicine and its alternative for the specified indications and other relevant information.

2.2 Cardiovascular Health Situation in the Americas

Cardiovascular diseases (CVD) are the main leading cause of death globally and accounts for 30% of deaths annually worldwide. In 2007, cardiovascular diseases caused 1.5 million deaths in the Region of the Americas where approximately 40% occur prematurely at an early stage of productive life. Among risk factors such as obesity, hypercholesterolemia and smoking, hypertension is the greatest risk factor for CVD and accounts for 62% of strokes and 49% of ischemic heart disease. Recent data states 18% of the adult population in Latin America suffers from hypertension. Therefore, the control of hypertension becomes the central focus in reducing cardiovascular disease risk.

Early detection and effective pharmacological treatments are crucial in order to reduce hypertension incidence and prevalence among the Region's population, but also to prevent further consequences such as stroke, acute coronary syndrome, congestive heart failure, and others. In low and middle income countries such as in the Americas, the best evidence-based approach for CVDs is a multidrug combination (aspirin, two antihypertensive medicine, and statins) for patients at high risk of cardiovascular disease or who already had a past cardiovascular event.

Considering these diseases and risk factors are more prevalent among poor populations and affect to a greater extend the vulnerable and socially disadvantaged, PAHO aims to increase access to quality medicines to prevent and treat cardiovascular diseases and decrease the financial burden they can represent.

3. Entity Supporting the Application and Requested Indications

3.1 Entity Supporting Application

The PAHO Noncommunicable Disease Unit (NMH/ND) is requesting and supporting this application.

3.2 Requested Indications

Lisinopril, an angiotensin converting enzyme (ACE) inhibitor, has been requested for the treatment of hypertension and heart failure in an adult population.

4. Medicine Characteristics and Pharmacological Information (*4–10*)

4.1 General Information

1) Medicine name (INN)	Lisinopril
2) ATC (anatomical therapeutic chemical- WHO Drug classification system)	C09AA03
3) Reference trade name: (1. Innovator & 2. Generic - when available some examples provided)	1. Innovator: Prinivil (Merck), also marketed as Zestril (AstraZeneca) 2. Generic: Lisinopril 5 & 20 mg (Mylan, Sandoz & others)
4) Therapeutic class (according to classification in the WHO EML)	This medicine is not present in WHO EML. The pharmacological class is Antihypertensive- Angiotensin Converting Enzyme Inhibitor (ACEi)

4.2 Mechanism of Action

Lisinopril is an inhibitor of the angiotensin converting enzyme, an enzyme that catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II stimulation on the adrenal cortex is also responsible for aldosterone secretion. Hence, inhibiting the angiotensin converting enzyme results in decreasing levels of angiotensin II leading to decreasing vasopressor effects and decreasing levels of aldosterone. Thus, lisinopril lowers blood pressure by suppressing the renin-angiotensin-aldosterone system.

4.3 Pharmacokinetic Considerations

- *Absorption:*
  - Following the oral absorption of lisinopril, the mean peak concentrations are reached after approximately 7 hours, but can be delayed in patients with acute myocardial infarction (8-10 hours). Lisinopril does not bind to other serum proteins. Based on urinary recovery, the medicine is absorbed at 25%, with a large inter-subject variability (6 to 60%) for all tested doses (5mg to 80mg). The bioavailability of the medicine is reduced to 16%in stable NYHA Class II-IV congestive heart failure patients. Food has no effect on the medicine's absorption.
- *Metabolism:*
  - Lisinopril does not undergo metabolism.
- *Elimination:*
  - The medicine is excreted totally unchanged in urine. The accumulation half-life after multiple dosing is 12 hours. Excretion can be altered by an impaired renal function; thus, increasing blood levels and exposure to the drug (increased area under plasma concentration-time curve).
- *Other:*
  - Studies in rats have demonstrated that lisinopril passes blood-brain barrier poorly and crosses the placenta. Also, lisinopril can be removed by hemodialysis.

4.4 Pharmacodynamics Considerations

The onset of antihypertensive activity is reached at around 6 hours after administration. The mean antihypertensive effect is lower 24 hours after dosing than it is 6 hours after dosing. It may take up to 2 to 4 weeks of therapy with lisinopril in order to reach the optimal blood pressure reduction. Abrupt withdrawal of the medicine does not result in a rapid increase in blood pressure. Some hemodynamic studies have showed that in patients with essential hypertension, along with blood pressure reduction, lisinopril reduces peripheral arterial resistance with negligible effect on cardiac output and heart rate. In patients with congestive heart failure, lisinopril increases cardiac output and exercise tolerance. Moreover, the ACEi effect on black patients is generally lower than in non-black patients.

4.5 Use in Specific Populations

- *Pediatric use:*
  - Based on available studies, lisinopril can be used in pediatric patients over 6 years old. Doses up to 40mg once daily have been studied in this hypertensive population aged 6 to 16 years old. There is no available data in patients under 6 years old or in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2.
- *Geriatric use:*
  - Caution with the dosing adjustments is required. In some conducted studies, no overall differences were identified between elderly and younger patients. However, most elderly patients have a decrease in renal, hepatic and/or cardiac function and have concomitant diseases and drug therapies. Therefore, a difference among this population cannot be ruled out. Because lisinopril is mainly excreted by the kidney, an evaluation of patients with hypertension, congestive heart failure, or myocardial infarction should include an assessment of the renal function to prevent toxicities.

- *Renal impairment:*
  - Dose adjustment is required. A decrease in renal function increases lisinopril blood concentrations. Consider lowering initial and maintenance dosage in patients with renal impairment to avoid renal and cardiac complications (see product monograph for doses according to creatinine clearance).

4.6 Dosage, Preparation and Administration

- *Dosage and Administration:*
  - Lisinopril is administered as a tablet, orally, once daily in the morning. It can be taken with or without food, consistently every day. Doses from 5mg once daily to a maximum of 80mg once daily have been used. The therapy should be monitored and the doses titrated every 2-3 weeks according to blood pressure response. Lower doses can be required in presence of diuretics or other antihypertensive drugs or in elderly and renal impaired patients. For patients at high risk of severe acute hypotension as patients with angina pectoris or cerebrovascular disease, the initiation of therapy and the titration should be done under the supervision of a physician until the patient is stable in order to avoid fall in blood pressure.
- *Hypertension:*
  - Lisinopril indicated in the treatment of hypertension can be used alone as initial therapy or in association with non-potassium sparing diuretics or other antihypertensive agents. An initial dosage of 5-10mg once daily is suggested. Doses can be titrated to 20- 40mg once daily. The maximum dosage is 80mg once daily.
- *Heart failure:*
  - Lisinopril is indicated as adjunctive therapy in the management of heart failure in patients not responding to a treatment with diuretic and, if appropriate, digitalis. Initial dose can start at 2.5-5mg once daily and be titrated slowly under medical supervision. Maintenance dose should be titrated with an increase of 2.5mg every 2-4 weeks to reach 5-20mg once daily. A maximum dose of 40mg is suggested.
- *Note:*
  - Lisinopril has also been used in the treatment of acute myocardial infarction, in combination with other standard recommended treatments for a period of 6 weeks, or more, if heart failure is present. It is also used in the treatment of renal disease in hypertensive patients with type II diabetes and nephropathy.

4.7 Contraindications

- Hypersensitivity to drug or any component or other ACEi
- Patient with a history of angioneurotic edema related to previous treatment with an ACEi
- Hereditary or idiopathic angioedema
- Co-administration with aliskiren-containing drugs in diabetic patients (type 1 or 2) or with moderate to severe renal impairment (GFR < 60 ml/min/1.73m2)
- Pregnancy/lactation
- Hemodynamic unstable patients after myocardial infarction

4.8 Warnings/Precautions

- *Use in pregnancy:*
  - Category D. ACE inhibitors must be discontinued as soon as possible when pregnancy is detected because of its fetal toxicity and neonatal morbidity and mortality. Exposure during 2nd and 3rd semester can lead to neonatal hypotension, neonatal skull hypoplasia, anuria, renal failure and oligohydramnios associated with craniofacial deformation and hypoplastic lung development. Cardiac and neurologic malformations have also been reported following exposure in the 1st semester.
- *Use in lactation:*
  - Presence in human milk has been reported. The use of ACEi is not recommended during breastfeeding.
- *Renal impairment:*
  - Appropriate assessment of renal function is required in patients whose renal function can depend on the renin-angiotensin-aldosterone system (bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, severe congestive heart failure). Changes in renal function for these patients can potentially lead to oliguria, progressive azotemia and rarely, acute renal failure and/or death.
- *Angioedema:*
  - Incidence of angioedema during ACEi therapy is higher in black patients than non-black patients. Angioedema can be fatal and when occurring, lisinopril must be discontinued immediately. If there is airway obstruction, emergency therapy should be administered immediately (epinephrine) and patient supervised until complete symptoms are resolved.
- *Hypotension:*
  - Patients with severe congestive heart failure, with or without renal insufficiency, patients with ischemic heart or cerebrovascular disease should be monitored closely by a physician because lisinopril can increase the risk of severe hypotension and lead to serious outcomes such as myocardial infarction or cerebrovascular accident. If severe hypotension occurs, it should be treated with appropriate treatments and lisinopril discontinued or reduced.
- *Neutropenia/agranulocytosis:*
  - Rare, but several cases reported. Caution is needed in patients with collagen vascular disease and renal disease and periodic monitoring of white blood cells considered.
- *Hypotension following acute myocardial infarction:*
  - Lisinopril must not be initiated in patients with cardiogenic shock or patients with blood pressure of 100mm Hg or less.
- *Hyperkalemia:*
  - Caution in patients with other risk factors (diabetes mellitus, renal insufficiency, use of potassium-sparing diuretics, potassium supplements or substitutes) as it can increase risk for hyperkalemia possibly leading to fatal arrhythmias.
- *Hypoglycemia:*
  - Caution in diabetic patients treated with antidiabetic agents or insulin and in patients with renal impairment. Concomitant use can increase risk of hypoglycemia, especially within the first month of use.

- *Patients with impaired liver function:*
  - Adverse effects such as hepatitis, jaundice, and elevation of serum bilirubin and/or liver enzymes have occurred. Most of the adverse effects are no longer observed once the drug was discontinued. Baseline liver function tests should be performed in patients with pre-existing liver abnormalities and close monitoring of the metabolic effects and drug response is required.
- *Valvular stenosis, hypertrophic cardiomyopathy:*
  - Lisinopril should be given with caution. Patients with these conditions can be at risk of decreased coronary perfusion when treated with vasodilators.

4.9 Side Effects

Common	Serious and rare:
• Dizziness • Headache • Asthenia/fatigue • Diarrhea • Dry cough • Hypotension	• Severe hypotension • Cardiovascular (myocardial infarction, cerebrovascular accident secondary to hypotension, tachycardia) • Dermatologic (Stevens-Johnson syndrome, erythema multiforme, pemphigus) • Endocrine (syndrome of inappropriate antidiuretic hormone secretion (SIADH)) • Gastro intestinal (abdominal pain, pancreatitis) • Hematologic (hemolytic anemia, agranulocytosis, anemia, thrombocytopenia) • Hepatic (jaundice, hepatitis, hepatic failure) • Metabolic (hypoglycemia) • Nervous system (paresthesia, mental confusion) • Respiratory (bronchospasm) • Urogenital (acute renal failure, oliguria/anuria) • And others

4.10 Main Interactions

Drug	Interaction
Aliskiren	Use is contraindicated in diabetic patients or in patients with moderate to severe renal impairment, can increase risk of renal impairment, hypotension and hyperkalemia.
Diuretics	Risk of hypotension. Risk of increased BUN and serum creatinine. Caution if concomitant use.
Agents increasing serum potassium	Caution if potassium sparing diuretics, potassium supplements or salt substitutes have to be administered for documented hypokalemia, monitor serum potassium frequently if co-administration.
Agents affecting sympathetic activity	Use with caution, beta-adrenergic blocking drugs can add to the antihypertensive effect.
Dual blockade of the RAS	Adding ACEi to an angiotensin receptor II antagonist can be associated to a higher incidence of hypotension, syncope, hyperkalemia and changes in renal function and this combination should be limited to specific cases.

continues

Drug	Interaction
Oral hypoglycemic agents and insulin	Increased hypoglycemic risk, use with caution.
Non steroid anti-inflammatory agents (NSAIDs) and COX-2 inhibitors	Can reduce antihypertensive effects, can precipitate acute renal failure if used in combination, monitor renal function
Lithium	Lithium elimination can be reduced, monitor lithium levels more frequently.
Gold (sodium aurothiomalate)	Concomitant use can lead to nitritoid reactions (facial flushing, nausea, vomiting, and hypotension).

4.11 Other

- *Photosensitive*
- *Laboratory monitoring:*
  - Serum electrolytes (hyperkalemia, hyponatremia), creatinine, blood urea nitrogen (BUN), liver enzymes and/or serum bilirubin should be monitored when initiating therapy and during maintenance therapy
- *Stability and storage recommendations:*
  - Lisinopril tablets should be stored at controlled room temperature 15-30°C (59-86°F), and protect from moisture.

5. Alternatives to Lisinopril Available in the Strategic Fund

The current version of the Strategic Fund medicine list includes enalapril as an alternative angiotensin converting enzyme inhibitor. Enalapril is also listed on WHO Essential Medicine List.

The following document provides the supporting evidence regarding the comparison of lisinopril and enalapril in the treatment of hypertension and heart failure in an adult population. This document does not represent a therapeutic guideline for treatment of these conditions and it is not intended for such use.

6. Guidelines Including the Use of the Medicine in Relation with the Proposed Indications

Below are presented some of the available guidelines for the treatment and management of hypertension and heart failure.

- National Clinical Guideline Center (NCGC): Hypertension - 2011
  http://www.nice.org.uk/nicemedia/live/13561/56007/56007.pdf
- European Society of Hypertension: Guidelines for the Management of Arterial Hypertension - 2007
  http://www.escardio.org/guidelines-surveys/esc-guidelines/guidelinesdocuments/guidelines-ah-ft.pdf
- National Heart, Lung, and Blood Institute (NHLBI): The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure - 2004
  http://www.nhlbi.nih.gov/guidelines/hypertension/index.html

7. Intervention and Summary of Evidence

The clinical questions presented below are based on the PAHO technical unit (NMH/ND) request to incorporate lisinopril in the Strategic Fund medicine list. The evidence summary presented in this section was developed in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb).

Due to the absence of systematic reviews for interventions in hypertension and heart failure (tables 7.1 & 7.2), the evidence presented is supported by a critical review of 5 and 2 clinical trials respectively.

The intervention and evidence summary have been compiled in two tables, with the corresponding characteristics of the critically reviewed trials and the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

The search strategy and references supporting the intervention and evidence summary are available in *Section 9* of this dossier.

7.1 Lisinopril Versus Enalapril in Adults with Hypertension

CLINICAL QUESTIONS
What is the compared efficacy, safety of lisinopril versus enalapril in the treatment of adult hypertension?

CONTEXT	Lisinopril versus enalapril
Lisinopril and enalapril are both angiotensin converting enzyme inhibitors (ACEIs) and are widely used in the treatment of hypertension. They are both suitable for once daily administration. It is important to ascertain whether there are any clinically relevant differences between lisinopril and enalapril in the treatment of adult hypertension.	

INTERVENTION	Lisinopril versus enalapril
Lisinopril does not show differences in reducing hypertension at short length of follow-up (up to 12 weeks) compared to enalapril. Very low quality evidence.	
Lisinopril does not show differences in adverse effects at short length of follow-up (up to 12 weeks) compared to enalapril. Very low quality evidence.	

Summary of evidence	
Benefits	The search did not retrieve systematic reviews assessing the effectiveness of lisinopril compared to enalapril in the treatment of adult hypertension. A specific search for trials found 5 clinical trials that performed a head to head comparison of these two treatments (*1-5*). One trial (*1*) compared the efficacy and safety of lisinopril (10 to 40 mg) and enalapril (5 to 20 mg) in 169 hypertensive patients during 12 weeks' treatment in a randomised double-blind parallel group study. After 12 weeks of treatment lisinopril produced a greater decrease in BP than enalapril (P<0.05). Sitting BP decreased by 25/15 mmHg on lisinopril and 17/12 mmHg with enalapril. Standing BP decreased by 24/14 mmHg compared with 16/10 mmHg on enalapril. Although a greater proportion of patients that received lisinopril (45 of 85; 51%) achieved the target BP (sitting DBP ≤90 mmHg) at week 12 compared with enalapril (35 or 84; 42%), the difference was not significant. Heart rate showed no significant change with the compared treatments.

continues

Summary of evidence	
Benefits *(cont.)*	A four-week double-blind, randomized parallel group study (*2*) compared daily doses of enalapril 20 mg with lisinopril 20 mg preceded by a 4-week single blind run-in period on placebo. Fifty-eight patients (49 males and 9 females, mean age 50.9) were recruited and 56 completed the study. Enalapril and lisinopril were equally effective in lowering blood pressure at rest, during dynamic and isometric exercise as well as during 24 h. The attained blood pressure levels during the early morning hours were for enalapril treatment 119/76 and 121/76 mmHg for lisinopril treatment. The ACE activity in serum 24 h post-dose was lower after treatment with lisinopril 8.0 (SD 3.3) µmol/min/1 than with enalapril 16.1 (SD 6.0) ($p < 0.001$). In a multicenter, double-blind, parallel-group, placebo-controlled study (*3*),after a two-week placebo run-in phase, 110 patients with mild to moderate hypertension were randomized to receive 10 mg lisinopril or enalapril, or placebo for 4 weeks. Office blood pressure was measured at regular intervals throughout the study. Twenty-four hour ambulatory blood pressure (ABP) was measured at baseline and after the first and final doses of study drug. Serum ACE activity and aldosterone were obtained concomitantly with each ABP monitoring. After four weeks of treatment, ABP analysis revealed that the lisinopril and enalapril groups, when compared with placebo, had similar and significant systolic and diastolic AUC reductions (P less than 0.01) from baseline over the 24 h dosing interval. During the second half of the dosing interval, 13-24 h post drug administration, the lisinopril group was significantly different from placebo (systolic BP, P = 0.002; diastolic BP, P = 0.005) while the enalapril group was not. One study (*4*) compared the antihypertensive effects of daily 10mg doses of the drugs in 13 patients using a randomised, double-blind, two period cross-over design with ambulatory blood pressure monitoring. Lisinopril lowered mean 24 hour systolic blood pressure significantly more than enalapril after 4 weeks of treatment (14/7 +/- 2/1mmHg & 9/6 +/- 2/1mmHg, respectively, adjusted SBP difference 4.8mmHg, $P < 0.01$). This difference was confined to the second 12 hours of the daily dosage interval (adjusted SBP difference 13-24 hours after dosing 9.9mmHg, $P < 0.001$). The diastolic pressure showed a similar trend but this was not statistically significant. In a single-blind, randomized cross-over study (*5*), 10 patients with mild to moderate hypertension were treated with either enalapril 10-20 mg once daily or lisinopril 10-20 mg once daily for two weeks. After two weeks' treatment, ambulatory blood pressure was assessed continuously for 48 hours. Blood pressure was significantly reduced by both ACE inhibitors and there was no difference between them. Ambulatory blood pressures over the whole 48 hours monitoring period and over the day time periods (7 am to 11 pm) were similar on both treatments except for day time diastolic pressure collected over 48 hours which was significantly lower ($p<0.05$; CI 95 % =0.1-8.7 mmHg) on lisinopril 87.2±7.0 mmHg) than enalapril (91.6±4.5 mmHg). The duration of effect of lisinopril (30.4 hours) was significantly greater than that of enalapril (20.7 hours). The proportion of ambulatory systolic and diastolic readings in excess of 140 or 90 mmHg respectively were greater for enalapril than for lisinopril: 55.9 % vs 46.5 % for systolic pressure on enalapril and lisinopril respectively ($p<0.001$) and 53.1% and 39.3% for diastolic pressure for enalapril and lisinopril respectively ($p < 0.001$).
Risks	One trial (*1*) compared the efficacy and safety profiles of lisinopril (10-40 mg) and enalapril (5-20 mg) in 169 hypertensive patients during 12 weeks' treatment in a randomised double-blind parallel group study. Fourteen patients withdrawn from the trial due to adverse events. In the lisinopril group 6 patients withdrew because of single cases of myocardial infarction, worsening angina, impotence, tiredness, headache and chest pain. The two serious adverse events, myocardial infarction and worsening angina were considered unrelated to drug therapy by the investigating physician. In the enalapril group 8 patients withdrew due to nausea/weakness (2 patients), palpitations/fatigue (2 patients), headache, ankle oedema, fatigue and reduced white cell count (in a white patient). In a four-week double-blind, randomized parallel group study (*2*) that compared daily doses of enalapril 20 mg with lisinopril 20 mg, 19 volunteered side-effects were reported after treatment with enalapril (n=28) as well as with lisinopril (n=28). Six patients (21%) in the former group and 7 (25%) in the latter experienced cough. In one multicentre, double-blind, parallel-group, placebo-controlled study (*3*) both drugs were well tolerated and only 5% of patients experienced adverse events, being the most frequents headache, asthenia, infection, pain, dizziness, dyspepsia and rash.

continues

Summary of evidence	
Risks *(cont.)*	In one study (*4*) that compared the antihypertensive effects of once daily 10 mg doses of the drugs in 13 patients the incidence of adverse experiences was similar with each drug. During treatment with lisinopril six subjects reported symptoms which included mild nausea, mild left iliac fossa pain, maculopapular rash in a patient with a chronic dermatological disorder; mild diarrhea lasting one day, onset of angina, and a febrile illness associated with splenomegaly that was thought to be viral in origin (1 case each). During treatment with enalapril, three subjects reported symptoms which comprised migrainous headaches, heartburn and rash (1 case each).
Comments/ Applicability	The available evidence for this clinical question comes from studies that included small numbers of patients and they could be underpowered to detect differences between treatments. The included trials did not describe in details the main aspects to judge their bias.
	The studies had short periods of follow-up, at most 12 weeks, and treatments are prescribed for long periods. That time frame is clearly insufficient to detect long term benefits or side effects.
	The studies evaluated the impact of the treatments on blood pressure, an intermediate outcome, instead on clinically relevant effects such as death or cardiovascular events.
	The trials did not included patients with co-morbidities which can be common in many elderly patients with hypertension, and did not pay attention to possible drug-interactions.
Cost studies	We have found a single study, published two decades ago, that assessed the cost-effectiveness of a voluntary program that switched enalapril to lisinopril therapy in patients with benign essential hypertension in a staff-model health maintenance organization (HMO) in the USA (*6*). The study was carried out in the context of a one-year non randomized, controlled trial. One hundred twenty-seven patients were entered into the study. 75 who converted from enalapril to lisinopril and 52 remained on enalapril throughout the study period. Patients taking enalapril were asked by staff pharmacists if they were willing to consider switching from enalapril to lisinopril. To encourage patients, the HMO agreed to waive the drug rider copayment for three months. If patients were willing, their physicians were contacted and they established the lisinopril dosage. Total direct cost and savings resulting from converting patients from enalapril to lisinopril were measured and compared with costs of therapy for patients who remained on enalapril. Drug acquisition costs, costs associated with waiving drug rider copayment, pharmacy administrative costs, costs of managing adverse events, costs of visits to physicians, and laboratory test costs were assessed. Depending on the cost of capital assumed, net savings ranged from US$ 85 to US$ 110 per patient converted from enalapril to lisinopril. Monthly net savings that ranged from US$ 2.04 to US$ 2.61 per patient were required to result in overall net savings within the first two years.

Table 1. Characteristics of Included Trials (*1-5*)

Study ID	Design (Sample size)	Patients	Intervention	Outcomes
Johnston 1991	Double blind, parallel RCT 169 patients	87 males, 82 females. Age: mean 57 years, range 25-85 Sitting BP (mmHg): 175/105 Standing BP (mmHg): 173/105	Lisinopril (10-40 mg) or enalapril (5-20 mg) for 12 weeks Target BP (sitting DBP ≤90 mmHg)	Primary Sitting BP (mmHg) Standing BP (mmHg)

continues

Study ID	Design (Sample size)	Patients	Intervention	Outcomes
Enstrom 1992	Double blind, parallel RCT 58 patients	49 males, 9 females Age: mean 50.9 years (Stand dev: 7.5) Systolic BP (mmHg): 163 (Stand dev:17) Diastolic BP (mmHg): 107 (Stand dev:8) BMI (kg/m2): 27 (Stand dev:4) BP at standardisation: 161/108 and 164/106 for enalapril and lisinopril, respectively.	Lisinopril (20 mg) or enalapril (20 mg) for 4 weeks	Primary: Blood pressure control at rest, during dynamic exercise test, during isometric exercise test, and during 24 h -with special focus on blood pressure control during the morning hours, 18-24 h post-dose.
Whelton 1992	Double blind, parallel RCT, placebo- controlled 110 patients	69 males, 41 females Age: mean 52 years, range 22-70 Baseline BP, average: 159/99	Lisinopril (10 mg) or enalapril (10 mg) or placebo for 4 weeks. Response: DBP ≤90 mmHg) or decrease in 10 mgHg	Primary: Office BPs Twenty-four hour ambulatory blood pressure (ABP) Secondary: Serum ACE activity and aldosterone
Gourlay 1993	Double blind, cross-over RCT 22 patients randomised, 13 for analysis	16 males, 6 females Age: mean 53 years, range 20-74 Baseline supine diastolic BP between 95 and 115 mmHg	Lisinopril (10 mg) or enalapril (10 mg) 4-5 weeks periods with a placebo wash-out period in the middle	Primary Ambulatory blood pressure monitoring
Plotquin 1993	Single blind, cross-over RCT 10 patients	9 males, 1 females Age: mean 56.4 years (SD 4.9), range 46-60 Baseline BP diastolic 106, systolic 161 mmHg Base line heart rate (bpm): 78	Lisinopril (10 mg) or enalapril (10 mg) in two weeks periods. After seven days the dose was increased to 20 mg once daily if sitting DBP was not ≤90 mmHg	Primary Ambulatory blood pressure monitoring over 48 hours

Table 2. GRADE Evaluation of Clinical Outcomes – Lisinopril Versus Enalapril in Patients with Hypertension (Assessment from Data in References *1-5*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
6 (394)	Changes in blood pressure	Lisinopril Enalapril	4	0	0	-1	-1	Low	Short follow-up periods, at most 12 weeks. Limited number of participants and events in each outcome
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

7.2 Lisinopril Versus Enalapril in Adults with Heart Failure

CLINICAL QUESTIONS
What is the compared efficacy, safety of lisinopril versus enalapril in the treatment of adult heart failure?

CONTEXT	Lisinopril versus enalapril
Congestive heart failure (CHF) is a chronic and increasingly common condition associated with substantial morbidity and mortality, as well as significant economic burden on the healthcare system worldwide, with an estimated prevalence of 3 to 20 per 1000 in the general population (*1,2*). Both the incidence and prevalence of CHF increase with age, from around 1% of those aged 50-59 years to 10% of those aged 80-89 years. This condition has a huge impact on patient's quality of life and carries a substantial risk of death; it has been reported that between a quarter and a third of patients will die one year after the onset of heart failure, and around two thirds of men and half of women will die after five years (*3*). The renin-angiotensin system (RAS) plays a vital role in the progression of heart failure. Therefore, two drug classes, ACE inhibitors and angiotensin receptor blockers (ARBs), were developed to inhibit the RAS and thus provide a potentially beneficial therapeutic approach for the treatment of heart failure. Therapies like angiotensin-converting enzyme inhibitors (ACE) reduce mortality and morbidity in chronic heart failure (*4*). ACE inhibitors have been indicated as first-line treatment for CHF (*5*) because they have been demonstrated in clinical trials evaluating morbidity and mortality to reduce mortality as well as rates of re-infarction and hospitalizations for heart failure.	

INTERVENTION	Lisinopril versus enalapril
Lisinopril does not show differences in exercise testing or duration, 24-hours Holter monitoring, NYHA classification, CHF symptomatology, blood pressure, heart rate, potassium concentration, renal function, left ventricular ejection fraction, ventricular ectopic beat counts, cardiothoracic ratio, rate of adverse effects or deaths compared to enalapril. Low quality evidence.	

Summary of evidence	
Benefits	The search did not retrieve systematic reviews assessing the effectiveness of lisinopril compared to enalapril in the treatment of adult heart failure. A specific search for trials found 2 clinical trials that performed a head to head comparison of these two treatments (*6,7*). The first study was a randomized, double blind, multicenter parallel groups trial involving a total of 278 patients, 138 allocated to a group that received lisinopril (19 women, 119 men) and 140 allocated to receive enalapril (27 women, 113 men). Groups were comparable at baseline with respect to age, body weight, baseline exercise capacity and the aethiology of the heart failure. Daily doses ranged in both groups between 5 and 20mg (*6*). The ZEBRAH study was a randomized double blind, double dummy, parallel groups trial involving a total of 251 patients, 127 receiving lisinopril (21% women, 79% men) and 124 enalapril (18% women, 82% men). Groups were comparable at baseline regarding age, body weight, blood pressure, heart rate, NYHA functional class, and the aethiology of heart failure (*7*). The Table 1 outlines the main characteristics of the studies considered. Zannad (*6*) assessed the following outcomes: exercise testing, 24-hours Holter monitoring, change with treatment in the NYHA Classification, symptoms review after 12 weeks of treatment, blood pressure and heart rate, blood chemistry and adverse events. The ZEBRAH study (*7*) assessed left ventricular ejection fraction, ventricular ectopic beats, exercise duration, NYHA status and cardiothoracic ratio.

continues

Summary of evidence	
Benefits *(Cont.)*	Zannad (*6*) did not show differences between lisinopril and enalapril in terms of exercise testing (Least-square mean increase in exercise duration at 6 weeks: lisinopril 30.1 seconds, enalapril 13.5 seconds, p = 0.14), or exercise duration at 12 weeks (Least-square mean increase in exercise duration: lisinopril 65.1 seconds, enalapril 41.9 seconds, p = 0.07). The trial assessed the outcome 24-hours Holter monitoring was using the parameters ventricular ectopic counts, nonsustained ventricular tachycardia, couplets and the reduction in the hourly rate of ventricular ectopic counts at week 12 compared to run-in values. No significant differences were detected regarding ventricular ectopic counts (p = 0.17), nonsustained ventricular tachycardia (p = 0.94), couplets (p = .09) and the reduction in the hourly rate of ventricular ectopic counts at week 12 (lisinopril group 52/83 [63%], enalapril group 51/88 [58%], p value not provided). The compared treatments did not show significant differences in terms of a change in the NYHA classification. There was an improvement of 48% in lisinopril group versus 43% in enalapril group, no change was observed in 49% in lisinopril group versus 53% in enalapril group, and there was deterioration in 3% of patients in lisinopril group versus 2% in enalapril group. With respect to the percentage of patients presenting with similar symptoms of CHF at the beginning of the study and after 12 weeks, lisinopril and enalapril improved the monitored symptoms, but the effect of treatments was similar with both drugs (no significance data provided). Blood pressure and heart rate were similar in both groups, and treatments have not significant changes on these parameters compared to baseline values (no significance data provided). No significant changes were observed in blood chemistry during the study. Authors pointed out that there was a tendency for potassium concentration to increase with both treatments. Renal function, measure by either serum creatinine or urea, did not change significantly with the treatments (no significance data provided). The ZEBRAH trial (*7*) did not show differences between lisinopril and enalapril in the increase from baseline in left ventricular ejection fraction (LVEF) (lisinopril 21.9% to 26.5 versus enalapril 20.3% to 24.3%, p<0.0001), or the change in ventricular ectopic beat counts (no data provided). The exercise test duration increased with both interventions, but difference between the drugs was not statistically significant (lisinopril 135.2 seconds versus enalapril 94.9 seconds, p<0.0001). Improvement in at least one grade in the NYHA functional class was observed in 69/127 patients in the lisinopril group and 65/124 in enalapril group, but the differences between groups were not statistically significant. Both groups showed a similar decrease in cardiothoracic ratio, from 0.56 to 0.53, regarding the baseline values.
Risks	Zannad (6) reported 15 patients withdrew lisinopril treatment, 8 cases due to adverse reactions. In the enalapril group, 14 patients withdrew, 12 of them because of adverse effects of the drug. Difference was not statistically significant. IN ZEBRAH (7) 68 patients withdrew from the study, 30 receiving lisinopril and 38 enalapril. The adverse events associated to the drugs were the main cause to withdraw in 25 patients from the lisinopril group and 26 in the enalapril group. During the treatment period in this study 69% patients that received lisinopril and 74% of patients in the enalapril group reported adverse effects related to the treatment, most of them were mild to moderate. Fourteen deaths were recorded in the study, 4 in lisinopril group, and 10 in enalapril group. None of these differences were statistically significant (statistical significance details not provided).

Summary of evidence	
Comments/ Applicability	The results from two double blind trials (6,7) failed to show a significant benefit of comparing lisinopril compared to enalapril. Both treatments have a similar efficacy profile in the management of moderate to severe congestive heart failure, with significant improvements in all the parameters measured when compared to baseline values. These findings are not surprising, as both drugs belong to the same class, and share similar mechanisms of action. With respect to safety, trials considered different outcomes, so that the conclusions drawn are based on the information coming from only one trial. The most commonly reported adverse effects were cough, dizziness, and fall in blood pressure, vertigo and myocardial infarction, with no differences between groups (6). Nonetheless, data should be interpreted with caution because of the small number of events in each group (between 1 and 4 events), so that the absence of difference in the analyses may result from a lack of statistical power, instead of an apparent similarity between the treatments.
	An additional weakness of the results obtained for this clinical question is the fact that only two trials were included, and that such trials considered different outcomes. Thus, it is not possible to make a pooled estimation of the effect of the interventions, which preclude from making a reliable judgment about the benefit of one treatment over the other.
	The applicability of these results is very limited due to the limited number of trials, participants and events in the analyses. The results suggest that both lisinopril and enalapril have a similar efficacy profile, and seems to have an acceptable safety, but these conclusions are based in findings of only two good-quality trials reporting different endpoints. Therefore, randomized controlled studies with standardized endpoints are needed to define the best option for the treatment of congestive heart failure.
Cost studies	The search did not retrieved relevant economic evaluations assessing the cost-effectiveness of lisinopril and enalapril in patients with heart failure.

Table 1. Characteristics of Included Trials (*6-7*)

Study ID	Design (Sample size)	Patients	Intervention	Outcomes
Zannad 1992	Double-blind, multicenter, parallel-groups RCT; n = 278, 138 in lisinopril group (19 women, 119 men), 140 in enalapril group (27 women, 113 men).	Male or female patients aged > 21 years, with signs and symptoms of congestive heart failure (CHF), on optimal dose of digitalis and/or diuretics, and capable of performing, with CHF confirmed by chest radiography, radioisotope scan or echocardiography. Groups were comparable regarding age, body weight, baseline exercise capacity, and aethiology of heart failure. The study was carried out in the Departments of Cardiology in France and The Netherlands.	Lisinopril versus enalapril. Starting dose 2.5 mg once daily. After a successful initiation of therapy, dose was increased to 5 mg once daily. If after 2 weeks clinical improvement was evident, treatment was maintained for the remainder of the study. If not, dose was increased to 10 mg once daily. At the end of 4 weeks of treatment the dose of the drugs could be doubled or decreased at any point during the study according to the evolution. Co-interventions were allowed if they were similar in both groups. Both treatment and follow-up lasted 12 weeks.	- Exercise testing - Holter monitoring - Change with treatment in the NYHA classification - Symptoms review after 12 weeks of treatment - Blood pressure and heart rate - Blood chemistry - Adverse events

Study ID	Design (Sample size)	Patients	Intervention	Outcomes
ZEBRAH 1993	Double blind, double dummy, parallel groups design RCT, n = 251, 127 in lisinopril group (21% women, 79% men), 124 in enalapril group (18% women, 82% men).	Male or female patients aged > 18 years, with signs and symptoms of CHF, NYHA classification III or IV, confirmed by clinical signs or symptoms and a left ventricular ejection fraction (LVEF) of less than 35% as measured by radioisotope imaging or left ventricle cine-angiography, capable of performing at least one minute of stand treadmill exercise test, and being in sinus rhythm or controlled atrial fibrillation. Groups were comparable regarding age, body weight, blood pressure, heart rate, NYHA functional class, and aethiology of heart failure. The study was carried out in 26 district general or university hospitals within the UK.	Lisinopril versus enalapril. Patients were sent home with a dose of 5.0 mg od. Concurrent therapies were permitted if remained constant during the study. Both treatment and follow-up lasted 6 months.	- Left ventricular ejection fraction - Ventricular ectopic beats - Exercise duration - NYHA status - Cardiothoracic ratio

Table 2. Grade Evaluation of Clinical Outcomes – Lisinopril Versus Enalapril in Patients with Heart Failure (Assessment from Data in Reference *6,7*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
2 (529)	Exercise testing	Lisinopril Enalapril	4	0	N/A	0	-2	Low	Data available from only two trials, with a limited number of participants and events in each outcome. Only p values provided.
2 (529)	NYHA status	Lisinopril Enalapril	4	0	N/A	0	-2	Low	Data available from only two trials, with a limited number of participants and events in each outcome.

Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion

8. Special Considerations and Additional Comments (*11-20*)

8.1 Regulatory Status of the Product in National Regulatory Authorities (NRAs)

The following table reflects the regulatory status of the product (innovator and generic – if applicable) in the 7 PAHO Region Reference NRAs (Argentina, Brazil, Canada, Colombia, Cuba, Mexico and United States) and the European Medicine Agency.

NRA	Status			
	5 mg Tab		20 mg Tab	
	Innovator	Generic	Innovator	Generic
Argentina (ANMAT)	x	x	x	x
Brazil (ANVISA)	x	x	x	x
Canada (Health Canada)	---	x	---	x
Colombia (INVIMA)	---	x	---	x
Cuba (CECMED)	x	x	x	x
Mexico (COFEPRIS)	x	x	x	x
USA (FDA)	x	x	x	x
Europe (EMA)	x	x	x	x

8.2 PAHO Member State Prices

Through ECONMED (an electronic listserv for public officials from the health sector), PAHO requested the price paid for procurement of lisinopril from Member States who utilize this products in their National Public Health Programs. Unfortunately, no data has been provided to PAHO by countries in Latin America and the Caribbean. PAHO will increase efforts to obtain some prices from Member States and will distribute the information when the committee convenes in Washington, D.C.

8.3 Results of PAHO Expression of Interest

For a medicine to be eligible for inclusion in the PAHO Strategic Fund medicine list, it must have supporting evidence of safety, efficacy, and clinical effectiveness. Additionally the product must satisfy one of the following criteria as related to the pharmaceutical market:

1. The acquisition of the medicines is subject to particular challenges related to product procurement, pricing, patent status, forecasting of future needs, and exclusivity contracts between pharmaceutical companies that restrict marketing in specific geographical areas.
2. Leveraging economies of scale (increases in the volume of medicine procured) can result in lower costs.

PAHO has established this criteria to ensure the inclusion of the product in the Strategic Fund will provide value added to Member States who procure this product through PAHO.

To evaluate these pharmaceutical market factors, the Procurement (PRO) Unit of PAHO conducted an Expression of Interest (EoI) to gather information related to the product. PRO contacted 19 suppliers, which are included in the PAHO approved supplier list, and asked for product data (i.e. available presentations, manufacturing origin & capacity, potential restrictions, prices, and available technical documents).

Limited response was obtained from the contacted suppliers; however, PRO believes lisinopril, does meet the pharmaceutical market criteria. Nonetheless, significant challenges are present and the following are key recommendations:

- Consolidate regional demand to leverage the benefits of economies of scale. If PAHO is able to obtain sufficient demand perform an international tender and establish Long Term Agreements with suppliers.
- Increase number of PAHO approved suppliers offering this product in order to ensure availability and create a more competitive market.

8.4 Potential Value Added for Procurement of the Medicine through the Strategic Fund

The current version of the Strategic Fund medicine list may limit treatment options of hypertension and heart failure, as the Fund only offers one ACE inhibitor (enalapril). If the presented evidence demonstrates adequate safety, efficacy, and clinical effectiveness, PAHO believes the inclusion of this product, will improve Member States access to an alternative ACE inhibitor that is effective and safe and can be used to reduce the burden of cardiovascular disease.

In comparison to enalapril, lisinopril is more expensive. For example, 2011 reference prices indicate lisinopril 20 mg Tab (US$ 0.0732 per unit) cost between 3-12 times more than enalapril (US$ 0.0107, US$ 0.0059 & US$ 0.0199 per unit for 5, 10 & 20 mg Tab). If included in the Strategic Fund List, PAHO would aim to consolidate regional demand to lower the costs of the product, thus easing the financial burden on Member States.

9. Search Strategy and References Supporting Intervention and Summary of Evidence

The interventions and evidence summaries presented in the two separate tables above in *Section VII.a-b* where all conducted with the same search strategy; however, each table yielded different results (selection criteria and the search strategy results). These differences are identified below is the table titled *Differences in the Selection Criteria and Search Results for each Clinical Question*. Additionally, the corresponding references for each clinical question are presented.

9.1 Inclusion Criteria

The aim of this evidence summary is to gather information from a systematic review about the benefits and risk of a drug in a specific health problem. For this reason we include in the summary the results from a rigorous systematic review, prioritizing Cochrane reviews. When a Cochrane review is not available or it is not suitable to respond the scope of the clinical question, we consider the inclusion of a systematic review that at least: i) includes a clearly defined inclusion criteria; ii) reports a recent search in at least two databases; and iii) reports any efforts from authors to assess the risk of bias from the included studies.

These criteria are the minimum requirements established by the Centre for Reviews and Dissemination to include a systematic review in the Database of Abstracts of Reviews of Effects (DARE; www.crd.york.ac.uk/crdweb/AboutPage.asp). For the specific purposes of the "Cost studies" section we include the results from an economic evaluation, that is; a comparison of two or more interventions or care alternatives (including cost-benefit analyses, cost-utility analyses, and cost-effectiveness analyses).

9.2 Search for Studies

The inclusion criteria described above determines the search for the studies planned. We design specific search algorithms to search the AHRQ Effective Health Care Program and The Cochrane Library as the main source to retrieve high quality systematic reviews. Each search in these two resources is complemented with a search in MEDLINE (accessed through PubMed) with the purpose of check any additional or more recent systematic review. The search is performed without any limitation, with the exception of PubMed in which we limit the search to the validated subset of systematic reviews (systematic[sb]). For the purposes of this clinical question no systematic reviews were available, and a specific search for clinical trials was designed to search the Cochrane Central Register of Controlled Trials. As we included only economic evaluations in the "Cost studies" section we limit the search to the NHS EED Database. In those cases that the NHS EED Database does not provide relevant results, we perform a specific search in MEDLINE, limiting the search algorithm designed to retrieve systematic review with the term cost*[tiab]. The search to develop the present clinical question was performed in May 2013, with the search strategies detailed below (Section 9.4).

9.3 Rating the Quality of the Evidence

Each evidence summary provides a rating of the quality of evidence following the GRADE guidance. GRADE specifies four categories (high, moderate, low, and very low) that are applied to the body of evidence that supports each assessed outcome. In the context of a synthesis of the evidence the quality of evidence reflects the confidence that the estimates of the effect are correct. For each clinical question one experienced researcher collects in a table the number of studies and patients included in these studies that set the body of evidence for each specific outcome discussed in the "Benefits" and "Risks" sections. The quality of evidence is then rated for each specific outcome and a final category is provided, commenting the main limitations that compromise the quality of evidence. All the information collected in the table, and the details required to the rating of the quality of evidence are obtained from the assessed systematic review used to develop the evidence summary.

9.4 Selection Criteria

One experienced researcher screens the results from the search applying the inclusion criteria commented above. If a Cochrane review is identified, it is selected to develop the evidence summary. When a Cochrane review is not suitable to respond to the scope of the formulated clinical question, the references from MEDLINE are screened. For the purposes of both clinical questions developed for lisinopril, no systematic reviews were available. Thus inclusion criteria focused in phase III randomized controlled trials, with blinding, including clinical outcomes, with a minimum duration of 4 weeks, and published in peer review journals.

Differences in the Selection Criteria and Search Results for each Clinical Question			
		Search strategy results	
Question	Selection criteria	Cochrane Database of Systematic Reviews: (The Cochrane Library; 5 of 12, May 2013)	MEDLINE (accessed via PubMed)
What is the compared efficacy, safety of lisinopril versus enalapril in the treatment of adult hypertension?	A search in the Cochrane Central Register of Controlled Trials and MEDLINE retrieved 76 references for clinical trials. The revision of their title and abstracts led to the exclusion of 62 references. We reviewed in detail 14 publications that resulted in the exclusion of 5 open label trials (*7-11*), 2 trials that assessed the benefits of treatments at short term (*12,13*), one trial compared single doses of treatments (*14*), and one did compared the two drugs of interest (*15*).	#1 lisinopril:ti,ab 741 hits #2 enalapril:ti,ab 1961 hits #3 #1 and #2 79 hits #4 MeSH descriptor: [Heart Failure] explode all trees 5033 hits #5 heart failure:ti 5658 hits #6 congestive cardiac failure:ti 758 hits #7 CHF:ti 124 hits #8 CCF:ti 3 hits #9 #4 or #5 or #6 or #7 or #8 6888 hits #10 MeSH descriptor: [Hypertension] explode all trees 13163 hits #11 hypertens*:ti 14998 hits #12 #10 or #11 19522 hits #13 #9 or #12 26215 hits #14 #3 and #13 52 hits	#37 lisinopril[tiab] 2012 hits #38 enalapril[tiab] 5497 hits #39 #37 AND #38 301 hits #40 "Heart Failure"[MeSH] 80963 hits #41 heart failure[ti] 42876 hits #42 congestive cardiac failure[ti] 281 hits #43 CHF[ti] 440 hits #44 CCF[ti] 48 hits #45 #40 or #41 or #42 or #43 or #44 87492 hits #46 "Hypertension"[MeSH] 201164 hits #47 hypertens*[ti] 152365 hits #48 #46 OR #47 240836 hits #49 #45 or #48 322592 hits #50 #39 AND #49 143 hits #51 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals[mh] NOT (humans[mh] AND animals[mh])) 784825 hits #52 #50 AND #51 66 hits
What is the compared efficacy, safety of lisinopril versus enalapril in the treatment of adult heart failure?	A search in the Cochrane Central Register of Controlled Trials and MEDLINE retrieved 76 references for clinical trials. The revision of their title and abstracts led to the exclusion of 70 references. We reviewed in detail 6 publications that resulted in the exclusion of a review of trials that compared ACE with placebo (*8*), a trial that compared the effect of an only dose of the drug at short term (*9*), a trial that compared the effects of two routes of administration (*10*), and a secondary publication of one of the included trials (*6,11*).		

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10. Additional References

The following references are those cited in Section 2 (Public Health Relevance), Section 4 (Medicine Characteristics and Pharmacological Information) and Section 8 (Special Considerations and Additional Comments). References supporting the intervention and summary of evidence are available in Sections 9.5 - 9.6.

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Annex 4

Review of the Available Evidence of Losartan Tablet (25, 50 & 100 mg) for Potential Inclusion in the Pan American Health Organization Strategic Fund Medicine List

Annex 4: Table of Contents

1. Introduction to the PAHO Strategic Fund

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (Strategic Fund) was created by the Director of the Pan American Health Organization (PAHO) at the request of Member States of the Organization, in September 1998 during the 35th session of the Pan American Sanitary Conference.

The Strategic Fund is a regional mechanism which aims to strengthen the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe and effective supplies at affordable prices obtained by leveraging the advantages of economies of scale.

To accomplish this objective the Strategic Fund publishes a list of medicines available for procurement in name of the Organization's Member States. The list utilizes as a foundation the World Health Organization (WHO) Essential Medicines List (EML); however, recently there has been a significant increase in Member State requests to procure products not included in the WHO EML.

In order to meet the needs of PAHO Member States the PAHO Director has created an external Expert Committee to review requests for inclusion of medicines not included in the WHO EML. This Expert Committee will allow PAHO to implement a decision making mechanism in agreement with concepts of quality, efficacy, safety and when available, information related to the value they provide in relation to their cost.

The committee will work exclusively on requests to update the SF medicine list, which will enable PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this EC should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

2. Public Health Relevance (*1-3*)

2.1 NCDs in the Region of the Americas

Over the last decades, noncommunicable diseases (NCDs) have become the leading cause of morbidity and mortality across the globe while imposing a growing threat to international development goals and economic growth as well as contributing to dramatic rises in health care expenditures.

The main NCDs principally include cardiovascular disease, cancer, diabetes and respiratory diseases and are accompanied by various common risk factors rising at a rapid pace. In the Americas region, NCDs are responsible for 3 out of every 4 deaths with cardiovascular diseases and cancer as the leading causes responsible respectively for 1.9 million and 1.2 million deaths each year. More than one third of these deaths are premature and occur in people under the age of 70 years old therefore leading to serious repercussions on social and economic development.

Noncommunicable diseases not only slow down development but also place a heavy financial burden on patients, healthcare and governments. The costs to overall health systems are expect to rise as governments are expected to increase funding to prevent and treat these diseases. Confronting the rising costs constitutes a real challenge in low and middle income countries of the Americas where economic growth is often compromised and healthcare systems have to manage access and equity issues. Patients are facing similar issues, as in many countries healthcare costs are paid out-of-pocket and the impact of NCDs on household budgets and healthcare expenditures can often lead to catastrophic spending and impoverishment.

In some countries of the region, out-of-pocket expenditures account for 78% of spending on medicines. Cardiovascular diseases constitute an important family expenditure on healthcare and can become an enormous economic and social burden in low-and-middle income countries. For example, patients suffering from more than two chronic diseases and taking more than two medicines for these conditions account for 10% of all patients in some countries. Health expenditures for this population can reach 50% of the overall health expenditure. Hence, in Latin America, out-of-pocket expenses related to NCDs and health expenditures accounting for chronic diseases represent a critical health care and financial issue.

In response to the NCD situation in the Americas, the 28th Pan American Sanitary Conference in September 2012, adopted the Regional Strategy for the Prevention and Control of Noncommunicable Diseases (Resolution CSP28.R13 aims to:

> "reorient and strengthen health systems to improve coverage, access to and quality of care provided to the people with NCDs or their risk factors, based on primary health care"

This process is linked with the WHO voluntary global NCD targets for 2025, which aims to achieve the following:

- 25% relative reduction of premature mortality due to noncommunicable diseases
- 80% coverage of essential NCD medicines and technologies
- 50% coverage of drug therapy and counseling.

As a critical component of PAHO's response to these issues, the Strategic Fund is increasing support and assistance to Member States by amplifying the list of NCD medicines for countries to procure. Thus, increasing access to quality drugs and helping ease the increasing financial burden, specifically for new or high cost medicines.

The Strategic Fund has initiated a process to review the available evidence regarding the efficacy, safety and cost-effectiveness of NCD medicines, particularly for cardiovascular diseases and cancer. The following document presents the status of the medicine, basic pharmacological information, the evidence comparing the requested medicine and its alternative for the specified indications and other relevant information.

2.2 Cardiovascular Health Situation in the Americas

Cardiovascular diseases (CVD) are the main leading cause of death globally and accounts for 30% of deaths annually worldwide. In 2007, cardiovascular diseases caused 1.5 million deaths in the Region of the Americas where approximately 40% occur prematurely at an early stage of productive life. Among risk factors such as obesity, hypercholesterolemia and smoking, hypertension is the greatest risk factor for CVD and accounts for 62% of strokes and 49% of ischemic heart disease. Recent data states 18% of the adult population in Latin America suffers from hypertension. Therefore, the control of hypertension becomes the central focus in reducing cardiovascular disease risk.

Early detection and effective pharmacological treatments are crucial in order to reduce hypertension incidence and prevalence among the Region's population, but also to prevent further consequences such as stroke, acute coronary syndrome, congestive heart failure, and others. In low and middle income countries such as in the Americas, the best evidence-based approach for CVDs is a multidrug combination (aspirin, two antihypertensive medicine, and statins) for patients at high risk of cardiovascular disease or who already had a past cardiovascular event.

Considering these diseases and risk factors are more prevalent among poor populations and affect to a greater extend the vulnerable and socially disadvantaged, PAHO aims to increase access to quality medicines to prevent and treat cardiovascular diseases and decrease the financial burden they can represent.

3. Entity Supporting the Application and Requested Indications

3.1 Entity Supporting Application

The PAHO Noncommunicable Disease Unit (NMH/ND) is requesting and supporting this application.

3.2 Requested Indications

Losartan, an angiotensin II receptor antagonists (ARA), has been requested for the treatment of hypertension, heart failure and type II diabetic patients with proteinuria and hypertension in an adult population.

4. Medicine Characteristics and Pharmacological Information (*4-9*)

4.1 General Information

1) Medicine name (INN)	Losartan potassium
2) ATC (anatomical therapeutic chemical- WHO Drug classification system)	C09CA01
3) Reference trade name: (1. Innovator & 2. Generic - when available some examples provided)	1. Innovator: Cozaar (Merck) 2. Generic: Losartan potassium 25, 50 & 100 mg (Teva, Sandoz & others)
4) Therapeutic class (according to classification in the WHO EML)	This medicine is not present in WHO EML. The pharmacological class is angiotensin II receptor antagonists (ARAs) also known as angiotensin receptor blockers (ARBs).

4.2 Mechanism of Action

Losartan potassium is an angiotensin II receptor antagonist that blocks vasoconstriction and secretion of aldosterone effects generated by angiotensin II by selectively binding to its type one (AT1) receptor found in various tissues (for example vascular smooth muscle, adrenal gland, etc.). Losartan (reversible competitive antagonist) and its active metabolite (reversible, non-competitive) have grater affinity for AT1 receptor than AT2.

4.3 Pharmacokinetic/Pharmacodynamics Considerations

- *Absorption:*
  - Following oral administration, losartan is well absorbed. The systemic bioavailability is 33% and 14% of losartan is converted to the active metabolite. The peak concentrations of losartan occur at approximately one hour and that of its metabolite around 3 to 4 hours.
- *Distribution:*
  - Losartan and its active metabolite are highly bound to plasma proteins. The volume of distribution of losartan is 34L and of the metabolite is 12L.
- *Metabolism:*
  - Losartan undergoes hepatic metabolism by cytochromes CYP450 mainly 2C9 and 3A4 and is converted into an active carboxylic acid metabolite. Other inactive metabolites are also formed.
- *Elimination:*
  - The elimination half-life of losartan is 2 hours and that of its metabolite 6 to 9 hours. The excretion of losartan is biliary (60%) and urinary (35%).

4.4 Use in Specific Populations

- *Pregnancy:*
  - Category D. Avoid use (see contraindication).
- *Lactation:*
  - It is not known whether losartan is excreted in human milk. Animal studies have shown excretion in rat milk. Considering the potential of excretion and the effect on the nursing infant, a decision should be made whether to discontinue nursing or to discontinue drug while considering the importance of the medicine for the mother.
- *Pediatric use:*
  - The pharmacokinetics of losartan proved to be similar in pediatric population to adult population. There is limited data available in pediatric patients with renal or hepatic impairment.
- *Geriatric use:*
  - No dosage adjustment necessary in the geriatric population. No differences in terms of safety were observed; however, caution should be used when prescribing considering the decrease of renal, hepatic and cardiac function and polytherapy in this population.
- *Renal impairment:*
  - Losartan directly affects the renin-angiotensin-aldosterone (RAA) system and this can represent a greater risk for patients whose renal function depend on it; such as patients with bilateral renal stenosis, unilateral renal stenosis to a solitary kidney, or severe congestive heart failure. Inhibiting the RAA system can lead to oliguria, progressive azotemia and rarely, acute renal failure and/or death in this population. The use of losartan requires appropriate renal assessment.
- *Hepatic impairment:*
  - Adjustment of dose needed. Consider lower dose in cirrhotic patients because of increase of plasma concentrations of losartan and its active metabolites.

4.5 Dosage, Preparation and Administration

- *Dosage and Administration:*
  - Losartan can be taken with or without food always consistently according to food intake and approximately at the same time every day.
- Losartan can be administered once or twice daily ranging from 25 to 100mg per day.
- *Hypertension:*
  - Individualize dosage for each patient (blood pressure (BP) value, other antihypertensive medicines, salt intake, and others). The initiating dose is 50mg once daily and maximum antihypertensive effect reached after 3 to 6 weeks. The usual maintenance dose ranges from 50mg to 100mg daily, the maximum dose. If patient is volume-depleted, consider a starting dose of 25 mg once daily. In patients that are receiving a concomitant diuretic therapy, diuretics should be discontinues 2 to 3 days prior or if continued, patient should be closely monitored for hypotension symptoms.
- *Type II Diabetes with proteinuria and hypertension:*
  - The usual starting dose is 50mg once daily and titrated to 100mg (maximum) according to therapeutic blood pressure response.
- *Hypertension with left ventricular hypertrophy:*
  - The usual starting dose is 50 mg once daily and increased according to blood pressure response to 100mg once daily. Hydrochlorothiazide is usually administered in concomitance.

4.6 Contraindications

- Hypersensitivity to drug or components
- Pregnancy: Discontinue losartan immediately if pregnancy is detected. Use of ARBs in the second and third semester can induce fetotoxicity on the fetus and neonatal toxicity.
- Co-administration of ARBs with aliskiren in patients with diabetes (type 1 or 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2).

4.7 Warnings/Precautions

- *Cardiovascular disease*
  - Risk of hypotension is increased in patients with cardiovascular disease as well as ischemic heart and cerebrovascular disease. Therapy should be initiated slowly and monitored closely in order to avoid important fall drop in blood pressure that could result in myocardial infarction or cerebrovascular accident.
- *Severe renal disease*
  - Losartan can precipitate azotemia and decrease glomerular filtration rate and can have cumulative effects with the progression of renal disease. If renal disease progresses, consider dose reduction or discontinuing thiazide therapy if co-administered.
- *Hepatic impairment*
  - May precipitate hepatic coma resulting in alterations in electrolyte balance. Dose adjustments are required.

- *Electrolyte disturbances*
  - Dilutional hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia may be aggravated and sometimes lead to serious adverse effects or toxicities (cardiac arrhythmias in cases of hypokalemia)

4.8 Side Effects

Common (clinical trials):	Serious and rare (from post market surveillance):
• Upper respiratory infection • Dizziness • Headache • Dry cough • Dyspepsia • Asthenia/Fatigue • Muscle pain/weakness/cramps	• Angioedema • Anaphylactic reactions • Severe hypotension/syncope • Myositis and rhabdomyolysis • Thrombocytopenia • Anemia • Hepatitis

4.9 Main Interactions

Drug	Interaction
Diuretics	Can increase hypotension risk
Agents increasing serum potassium	Potassium-sparing diuretics (spironolactone, triamterene, amiloride), potassium supplements or salt substitutes can increase potassium levels and lead to hyperkalemia
RAS-Renin Angiotensin System blockade with ARB's, ACEIs or aliskiren containing drugs	This combination is contraindicated in patients with diabetes and/or renal impairment
Lithium	Lithium excretion can be reduced
Non steroid anti-inflammatory agents (NSAIDs) including COX-2 inhibitors	Can reduce antihypertensive effects, can precipitate acute renal failure if used in combination, monitor renal function
Drugs affecting the P450 system	Inductors (rifampin) can decrease level of active metabolite and inhibitors of CYP450 2C9 can decrease active metabolite concentration and increases losartan concentration (ex: fluconazole)

4.10 Other

- *Patient counseling*
  - Inform patient of pregnancy risks and suggest reporting pregnancy to their physician immediately. Instruct patients to consult a physician before consuming any product containing K+.
- *Storage*
  - Store at room temperature 25°C (77°F), permitted 15°C -30°C (59°F -86°F), Protect from light. Keep container tightly closed.
- *Monitoring*
  - Laboratory monitoring for creatinine, kalemia, blood urea nitrogen, liver function tests (hepatic impairment) and monitoring of blood pressure during therapy is required

5. Alternatives to Losartan Available in the Strategic Fund

The Strategic Fund list does not currently offer any medicines classified as angiotensin II receptor antagonists (ARAs). The WHO Essential Medicine List is also lacking any medicines in this pharmacological class.

The following document provides the supporting evidence regarding the comparison of losartan and valsartan in the treatment of hypertension, heart failure and type II diabetic patients with proteinuria and hypertension in an adult population. This document does not represent a therapeutic guideline for treatment of these conditions and it is not intended for such use.

6. Guidelines Including the Use of the Medicine in Relation with the Proposed Indications

Below are presented some of the available guidelines for the treatment and management of hypertension and heart failure.

- National Clinical Guideline Center (NCGC): Hypertension - 2011
  http://www.nice.org.uk/nicemedia/live/13561/56007/56007.pdf
- European Society of Hypertension: Guidelines for the Management of Arterial Hypertension - 2007
  http://www.escardio.org/guidelines-surveys/esc-guidelines/guidelinesdocuments/guidelines-ahft.pdf
- National Heart, Lung, and Blood Institute (NHLBI): The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure - 2004
  http://www.nhlbi.nih.gov/guidelines/hypertension/index.html

7. Intervention and Summary of Evidence

The clinical questions presented below are based on the PAHO technical unit (NMH/ND) request to incorporate losartan in the Strategic Fund medicine list. The evidence summary presented in this section was developed in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb).

The intervention and evidence summary has been compiled in three tables (*7.1-7.3*), with the corresponding Grading of Recommendations Assessment, Development and Evaluation (GRADE) and when relevant additional tables and figures.

The evidence presented for interventions in hypertension (*Table 7.1*) is supported by a systematic review. Due to the absence of systematic reviews for interventions in hypertension associated with type II diabetes proteinuria and heart failure (*Tables 7.2 & 7.3*), the evidence presented is supported by a different search strategy.

The evidence presented in *Table 7.2* (hypertension associated with type II diabetes with proteinuria) is supported by a critical review of 1 clinical trial.

The search strategy employed to support the evidence presented in *Table 7.3* (heart failure) did not identify studies with a head to head comparison of losartan compared to valsartan in adult heart failure. As a result, data from clinical trials included in a Cochrane Systematic Review comparing losartan and valsartan versus placebos was used to support the evidence summary.

The search strategy and references supporting the three interventions and evidence summaries are available in *Section 9* of this dossier.

7.1 Losartan Versus Valsartan in Adults with Hypertension

CLINICAL QUESTIONS
What is the compared efficacy and safety of losartan versus valsartan in adult hypertension treatment?

CONTEXT	Losartan versus valsartan
Hypertension affects approximately one billion adults worldwide. It is a major risk for cardiovascular diseases and stroke, and it is associated with metabolic syndromes including insulin resistance and lipid abnormalities. The high prevalence of hypertension has contributed to the present pandemic of CV disease, which now accounts for 30% of all deaths worldwide (*1*) The treatment of hypertension is a major contribution to the decline in the incidence of stroke and heart disease over the past 30 years. Frequently cited data from phase II (1992 to 1994) of the third National Health and Nutrition Examination Survey (NHANES III) indicate that 32 percent of all persons with hypertension are unaware of their condition and are not receiving treatment, 15 percent are aware of it but are not receiving treatment, and 26 percent have treated but uncontrolled hypertension, leaving only 27 percent in whom hypertension is controlled (*2*). The rennin-angiotensin-aldosterone-system (RAAS) plays an integral role in the pathophysiology of hypertension, functioning as a primary regulator in the control of fluid volume, electrolyte balance and blood volume. In conjunction, angiotensin II causes potent vasoconstriction, aldosterone secretion and sympathetic activation, all of which contribute to the development of hypertension. There are currently six angiotensin II receptor blockers used as first line treatment in hypertension: valsartan, candesartan, irbesartan, losartan, olmesartan and telmisartan (*1*).	

INTERVENTION	Losartan versus valsartan
Valsartan is more effective than losartan in lowering the mean blood pressure in patients with hypertension. Low quality evidence.	
Angiotensin II receptor blockers reduce the rate of trial withdrawals due to adverse effects compared with placebo. Low quality evidence.	

Summary of evidence	
Benefits	A systematic review was found (date of search: May 2008) (*1*). The review aimed to compare the efficacy of valsartan in reducing systolic (SBP) and diastolic blood pressure (DBP) with other angiotensin II receptor blockers (ARBs) in essential hypertension. The review included a total of 31 randomised double blind controlled trials accounting for 13,110 patients. The studies included the following ARBs: candesartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. Authors extracted the following information from trials to construct the meta-analytical models: i) the estimate of the mean change in blood pressure (BP) from baseline to follow-up; ii) the standard deviation (SD) of this change; iii) the estimate of the mean BP at baseline and the number of patients randomized. A random-effect meta-regression model was used to estimate the overall mean change in systolic (SBP) and diastolic BP (DBP) from baseline to follow-up. The model adjusted the estimate of the overall mean change in BP for the baseline BP. The authors did not identify trials comparing head to head losartan and valsartan and reported data for the changes in BP for the two ARBs in separate and finally estimated indirect comparisons. Valsartan showed a large change in dose-response when doses were increased from 80mg to 160mg and above. Mean change in SBP for valsartan 80, 160 and 320 mg increased from -11.52 (95% CI: -14.39, -8.70) to -15.32 mmHg (95% CI: -17.09, -13.63) to a further -15.85 mmHg (95% CI: -17.60, -14.12). For DBP, this increase was -8.71 mmHg (95% CI: -9.94, -7.50) to -11.33mmHg (95% CI: -12.15, -10.52) to a further -11.97 mmHg (95% CI: -12.81, -11.16). The weighted average reduction in mean SBP and DBP for losartan 100mg was -12.01 mmHg (95% CI: -13.78, -10.25) and -9.37mmHg (95% CI: -10.18, -8.54) respectively.

continues

Summary of evidence	
Benefits *(cont.)*	The authors obtained indirect comparisons of mean change from baseline in SBP and DBP by drug and dose. A greater reduction in BP with valsartan 160mg and 320mg was statically significant compared with losartan 100mg. Indirect comparisons demonstrated greater mean change in SBP and DBP from baseline in favour of valsartan 160mg over losartan 100mg: 3.31 mmHg (95% CI: 0.86, 5.79) and 1.95 mmHg (95% CI: 0.81, 3.11). No significant difference in BP reduction was observed for valsartan 80mg compared with losartan 50mg: the difference in the mean change in SBP is 1.59 mmHg (95% CI: -2.44, 5.69) and for DBP is 0.67 mmHg (95% CI: -0.95, 2.35).
Risks	The review commented above did not discuss data on adverse effects of the included ARBs. A Cochrane systematic review (*3*) assessed the effectiveness and safety of ARBs (including losartan and valsartan) in patients with hypertension. The review aimed to assess the rate of trial withdrawals due to adverse effects (WDAE), but only half of included studies reported data on this outcome and they included insufficient data to evaluate the dose-related effect of the individual ARBs. The available data showed that all doses ARBs resulted in a reduction in WDAE compared with placebo (RR 0.68; 95%CI 0.54 to 0.87).
Comments/ Applicability	The assessed systematic review (*1*) focused its interest in the changes of ARBs in BP, omitting important outcomes for patients such as those related with cardiovascular risk reduction (heart failure, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke), or patient tolerability (adverse events).
	The review failed to identify head to head comparisons between losartan and valsartan, limiting the applicability of the available evidence to decide if valsartan could be preferred over losartan for hypertension treatment.
	The clinical application of these results could be limited by the inclusion and exclusion criteria applied. Results were confined to monotherapy, whereas many patients in clinical practice receive combination therapy.
	The assessed systematic review was sponsored by Novartis.
Cost studies	A cost-effectiveness study was found (*4*). Its objective was to evaluate the cost-effectiveness of valsartan, compared with losartan, and the impact of switching patients from valsartan to generic losartan, to lower blood pressure and prevent cardiovascular disease. A Markov model was used to simulate the patient's progression through clinically relevant health states, and assess the cost and outcomes associated with those states, for the three interventions. The time horizon was 20 years. The authors stated that the perspective was that of the third-party payer. Valsartan appeared to be cost-effective, compared with switching to generic losartan. Overall the quality of the study was adequate, but some of the assumptions were limited due to a lack of data.

Table 1. Grade Evaluation of Clinical Outcomes – Losartan Versus Valsartan in Adults with Hypertension (Assessment from Data in Reference *1*)

Number of studies (N))	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
Valsartan 14 (6752) Losartan 8 (1856)	Change from baseline in SBP and DBP by drug and dose (reference 1)	Valsartan Losartan	4	0	0	-2	0	Low	No head to head comparisons available, the results were based in indirect assumptions
ARBs 26 (9585)	Rate of trial withdrawals due to adverse effects (reference 3)	ARBs Placebo	4	0	0	-2	0	Low	No head to head comparisons available, the results were based in indirect assumptions

Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion

7.2 Losartan Versus Valsartan in Adults with Hypertension Associated with Type II Diabetes with Proteinuria

CLINICAL QUESTIONS
What is the compared efficacy and safety of losartan versus valsartan in adult hypertension associated with type 2 diabetes with proteinuria?

CONTEXT	Losartan versus valsartan

Microalbuminuria is not only a sign of the progression of renal impairment, but is also an independent risk factor for cardiovascular disease. Microalbuminuria is present in approximately 50% in patients with type 2 diabetes. Moreover, its frequency rise as the severity of hypertension increases, suggesting that the frequency of microalbuminuria in patients with type 2 diabetes and hypertension is very high. Since renal and cardiovascular risk in these patients is high, aggressive therapy is necessary from an early stage. Strict glycaemic and blood pressure control by the inhibition of the renin-angiotensin system (RAS) in the microalbuminuric stage has been suggested in order to inhibit the transition to manifest nephropathy and to normalize microalbuminuria (*1*).

Angiotensin-II-receptor blockers (ARBs) are primarily prescribed as antihypertensive drugs, and several guidelines recommend these agents as first-line therapy for patients with arterial hypertension. The benefits of ARBs extend, however, beyond lowering of blood pressure. Their use to selectively inhibit the angiotensin II type 1 (AT1) receptor can protect against the progression of kidney disease (*2*).

INTERVENTION	Losartan versus valsartan

Losartan does not show differences in systolic/diastolic blood pressure or creatinine clearance compared to valsartan.

Very low quality evidence.

Summary of evidence	
Benefits	The search did not retrieve systematic reviews assessing the effectiveness of losartan compared to valsartan in the treatment of hypertension associated with type 2 diabetes with proteinuria. A specific search for trials found a unique clinical trial that performed a head to head comparison of these two treatments (*1*). In this trial, 80 subjects with concomitant type 2 diabetes and hypertension were diagnosed with early nephropathy (stage 2) at the outpatient clinic of two institutions. Patients in this study were adults and their characteristics are outlined in the table 1. A causal blood pressure measured at the outpatient clinic of 140/90 mmHg or higher was diagnosed as hypertension. Patients undergoing diet and exercise therapy were selected. The criterion for early nephropathy was 30-299 mg/day urinary albumin in 24-h urine. Patients were allocated in 4 groups of 20 for treatment with telmisartan, valsartan, candesartan or losartan, and were prospectively followed for 12 months. Causal blood pressure at the outpatient clinic, the serum creatinine level, creatinine clearance and urinary albumin level were measured before test drug administration (baseline) and 2, 4, 6 and 12 months of treatment. HbA1c was measured before and after 12 months of treatment. At 12 months, the mean doses of valsartan and losartan were 116.0 +/- 40.8 and 71.3 +/-21.9 mg/day, respectively. After 12 months of treatment, no significant differences were noted in the systolic/diastolic blood pressure, creatinine clearance or serum creatinine levels of valsartan and losartan (results collected in table 2). The trial did not specify results regarding differences between groups. The authors reported that patients achieved the blood pressure target values in all groups, without differences between groups. The urinary albumin level was decreased in all groups, but the decrease from baseline was significant only telmisartan group.
Risks	The assessed trial (*1*) did not show data regarding adverse effects from compared treatments. The authors only included the following comment: "No adverse effects necessitated the discontinuation of test drug administration, and all test drugs were well tolerated".
Comments/ Applicability	The lack of data from head to head comparisons of losartan and valsartan in adults with hypertension with type II diabetes with proteinuria limits the applicability of the available evidence to decide if any of these angiotensin receptor blockers could be preferred over the other. On the other hand some aspects from the assessed trial make the interpretation of it is results and it is applicability to a wider community difficult. The unavailability of specific comparisons between the drugs compared and the limited sample size precludes firm conclusions (*1*).
Cost studies	The search did not retrieved relevant economic evaluations assessing the cost-effectiveness of losartan and valsartan in patients with hypertension related to diabetes type 2 proteinuria.

Table 1. Characteristics (Demographics) of Included Trial (*1*)

	Telmisartan (n=20)	Valsartan (n=20)	Candesartan (n=20)	Losartan (n=20)
Age (years)	74.3 +/- 4.4	73.6 +/-5.0	73.3 +/-5.5	72.6 +/-4.7
No. male (%)	10 (50)	10 (50)	10 (50)	10 (50)
No. statin (%)	2 (10)	1 (5)	3 (15)	2 (10)

Table 2. Changes from Baseline for the Drugs of Interest in the Included Trial (*1*)

Variable	Valsartan (n=20)			Losartan (n=20)		
	Baseline	12 months	p-value	Baseline	12 months	p-value
Systolic blood pressure (mmHg)	176.4 +/- 9.4	128.2 +/- 1.8	<0.001	176.9 +/- 7.2	128.5 +/- 2.0	<0.001
Diastolic blood pressure (mmHg)	85.0 +/- 5.6	72.6 +/- 4.3	<0.01	86.3 +/- 5.2	70.1 +/- 5.9	<0.001
Creatinine clearance (ml/min)	68.2 +/- 10.8	62.5 +/- 9.0	0.004	71.0 +/- 9.8	61.1 +/-10.4	<0.001
Serum creatinine (mg/ml)	1.20 +/- 0.04	1.27 +/-0.03	<0.001	1.20 +/- 0.03	1.26 +/-0.02	<0.001
Urinary albumin excretion (mg/day)	80.0 +/- 17.2	66.0 +/- 27.7	0.043	80.8 +/- 19.2	74.2 +/- 31.5	0.204
HbA1c (%)	6.2 +/- 0.2	6.2 +/- 0.2	0.204	6.3 +/- 0.2	6.2 +/- 0.2	0.800

Table 3. Grade Evaluation of Clinical Outcomes – Losartan and Valsartan in Patients with Hypertension Related to Diabetes Type 2 with Proteinuria (Assessment from Data in Reference *1*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
1 (80)	Systolic/ diastolic blood apressure Creatinine clearance Serum creatinine Urinary albumin	Valsartan Losartan	4	-1	0	-1	-1	Very low	QUALITY: It is not clear if the evaluators were blinded and which was the method of randomization. DIRECT EVIDENCE: analysis included all angiotensin receptor blockers PRECISION: event rate very low and small sample size

Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion

7.3 Losartan Versus Valsartan in Adults with Heart Failure

CLINICAL QUESTIONS
What is the compared efficacy and safety of losartan versus valsartan in adult heart failure treatment?

CONTEXT	Losartan versus valsartan

Chronic heart failure (CHF) is a serious condition associated with high morbidity and mortality rates all over the world. The incidence of CHF is approaching 10 per 1000 population after 65 years of age and CHF is the largest diagnosis related group (DRG) in the USA among persons aged more than 65 years, contributing to 20% of all hospitalizations (*1*).

Angiotensin converting enzyme inhibitors (ACEIs) are the recommended agents for all stages of CHF, but in recent years, the use of angiotensin receptor blockers (ARBs), such as losartan and valsartan is increasing due to their better tolerability. ARBs have been proven for their clinical effectiveness in CHF in randomized clinical trials against placebo and ACEIs, but they have yet to be compared head to head in an RCT. With an assumption of therapeutic class effect, these agents are used interchangeably in routine clinical practice. However, ARBs are heterogeneous non peptide drugs that differ noticeably in their pharmacokinetic and pharmacodynamic properties. Several RCTs have been conducted to compare these agents head to head for their efficacy in hypertension, and they have revealed some differences in their efficacy. It is unlikely that a clinical trial will compare four ARBs in near future for CHF because of the enormous size, expense, and time such comparative trials of survival would entail.

INTERVENTION	Losartan versus valsartan
Losartan does not show differences in all-cause mortality compared to valsartan. *Very low quality evidence.*	

Summary of evidence	
Benefits	A Cochrane systematic review (*2*) assessed the benefits and harms of angiotensin receptor blockers (ARBs), such as losartan and valsartan, compared with ACE inhibitors or placebo on mortality, morbidity and withdrawals due to adverse effects in patients with symptomatic heart failure and left ventricular systolic dysfunction or preserved systolic function. The review included 22 trials that evaluated the effects of ARBs in 17,900 patients with a LVEF ≤40% (mean follow up of 2.2 years in the largest studies). However the review did not identified head to head comparisons of losartan compared to valsartan, and a specific search for trials neither identified any relevant controlled trial comparing these two drugs. The Cochrane review (*2*) included 3 trials that compared losartan versus placebo (552 patients) and 4 studies comparing valsartan versus placebo (5,545 patients). The review provided enough data to pool the data from the studies controlled with placebo for the outcome total mortality using a fixed effects model (figure 1). The results from one trial that compared valsartan versus placebo did not show differences in total mortality (101 patients, 2 events; RR 0.35; 95%CI 0.02 to 5.35). On the other hand losartan showed a significant reduction of mortality compared with placebo (3 RCT; 890 patients, 24 events; RR 0.35; 95%CI 0.15 to 0.80). Despite this significant result for losartan, the results for valsartan can be explained by the limited sample size and events observed, and an indirect comparison suggests no differences between losartan and valsartan in reducing total mortality. In an effort to obtain data from direct comparisons of losartan and valsartan two retrospective studies with a large sample were identified (*1,3*). A retrospective analysis was conducted on a national sample of patients diagnosed with CHF identified from Veterans Affairs electronic medical records in the USA (*1*), with supplemental clinical data obtained from chart review. After excluding patients with exposure to ARBs within the previous 6 months, four treatment groups were defined based on initial use of candesartan, valsartan, losartan, and irbesartan. Time to death was measured concurrently during that period. A marginal structural model controlled for socio-demographic factors, comorbidities, co-medications, disease severity (left ventricular ejection fraction), and potential time-varying confounding affected by previous treatment (hospitalization). Propensity scores derived from a multinomial logistic regression were used as inverse probability of treatment weights in a generalized estimating equation to estimate causal effects. Among the 1,536 patients identified on ARB therapy in this study, irbesartan was the drug most frequently used (55.21%), followed by losartan (21.74%), candesartan (15.23%), and valsartan (7.81%). After an adjustment for time-varying hospitalization in a marginal structural model, losartan, candesartan (OR = 0.79, 95%CI: 0.42 to 1.50), irbesartan (OR = 1.17, 95%CI: 0.72 to 1.90), and valsartan (OR =0.98, 95%CI: 0.45 to 2.14) showed a similar effectiveness in reducing mortality in CHF patients. A Canadian retrospective population-based study examined the class effect of angiotensin II receptor blockers (ARBs) on mortality in patients with heart failure who were aged 65 years or older using administrative database related to hospital discharge summaries for the Canadian provinces of Quebec, Ontario, and British Columbia (3). They study provided data for 6,876 patients aged 65 years or older who were discharged with a primary diagnosis of heart failure and who filled at least one prescription for an ARB within 90 days of discharge. The patients had a mean +/- SD age of 78 +/- 7 years, and most (62%) were women. Losartan was the most frequently prescribed ARB (61%), followed by irbesartan (14%), valsartan (13%), candesartan (10%), and telmisartan (2%). Times to all-cause death in patients receiving individual ARBs were compared. Models were adjusted for demographic, clinical, physician, and hospital characteristics; models were also adjusted for dosage categories, which were represented by time-dependent variables. The study showed that valsartan was associated with better survival rates than losartan (adjusted HR 0.63; 95%CI: 0.51 to 0.79).
Risks	As commented above, in the absence of direct comparisons between losartan and valsartan, we obtained data from a Cochrane review that compared the drugs of interest against placebo (*2*). The review assessed withdrawals due to adverse effects, but information on that outcome was only available for one RCT that compared valsartan and placebo. There were 2 withdrawals out of 75 patients taking valsartan for none in the 26 patients taking placebo (101 patients; RR 1.78; 95%IC: 0.09 to 35.84) (figure 2). None of the studies that compared losartan versus placebo provided information on withdrawals due to adverse effects.

Summary of evidence	
Comments/ Applicability	There is no direct evidence from controlled trials with head to head comparisons between losartan and valsartan. This circumstance limits seriously the applicability of the available evidence to decide if any of these drugs could be preferred over the other. In the other hand, as the Cochrane review (*2*) revealed, there are several other significant limitations in the available evidence from trials, including the studies that compared losartan or valsartan with placebo, most notably related with the poor reporting of methodology in many publications. The method of randomisation, allocation concealment, and blinding was rarely described. Although the quality of reporting tended to be better in long-term health outcome studies, details on the methodology were still incomplete. Almost all the included studies were sponsored by the manufacturer making a high risk of publication bias and other biases likely. Therefore, it is possible that the inability to identify unpublished studies with negative results may have led to overestimation of treatment effects in that review. Furthermore, the meta-analysis may under-estimate the harms associated with ARB therapy as a result of patient selection bias. In some trials in HF patients with preserved systolic function, participants with a previously documented intolerance of ARBs were excluded. This source of bias clearly influenced the outcome of withdrawals due to adverse effects.
	Available evidence coming from retrospective studies with a large sample (*1,3*) is considered of low quality and can be subject to other potential relevant biases such as patient selection, which also compromises the generalizability of their results to different populations of patients. For instance, one of the studies was done on a sample of a specific population, those in the Veterans Affairs electronic medical records in the USA (*1*).
	It is important to note that ARBs do not reduce total mortality or all-cause hospitalisations compared with placebo in the treatment of HF patients irrespective of LVEF. In the Cochrane review (*2*) commented that in patients with LVEF ≤40%, the benefit observed with ARBs in terms of a reduction in hospitalisations for HF was mitigated by an increase in hospitalisations for other causes. More patients treated with ARBs stopped treatment early due to adverse effects compared with placebo. The main challenge in comparison of true treatment (causal) effects in an observational study is the presence of confounding, especially confounding by indication for treatment. Furthermore, in longitudinal studies involving chronic illnesses such as CHF, some confounders change with time during the follow up.
Cost studies	The search did not retrieved relevant economic evaluations assessing the cost-effectiveness of losartan and valsartan in patients with heart failure.

Figure 1: Pooled Result for Total Mortality (Obtained from Data in Reference *2*)

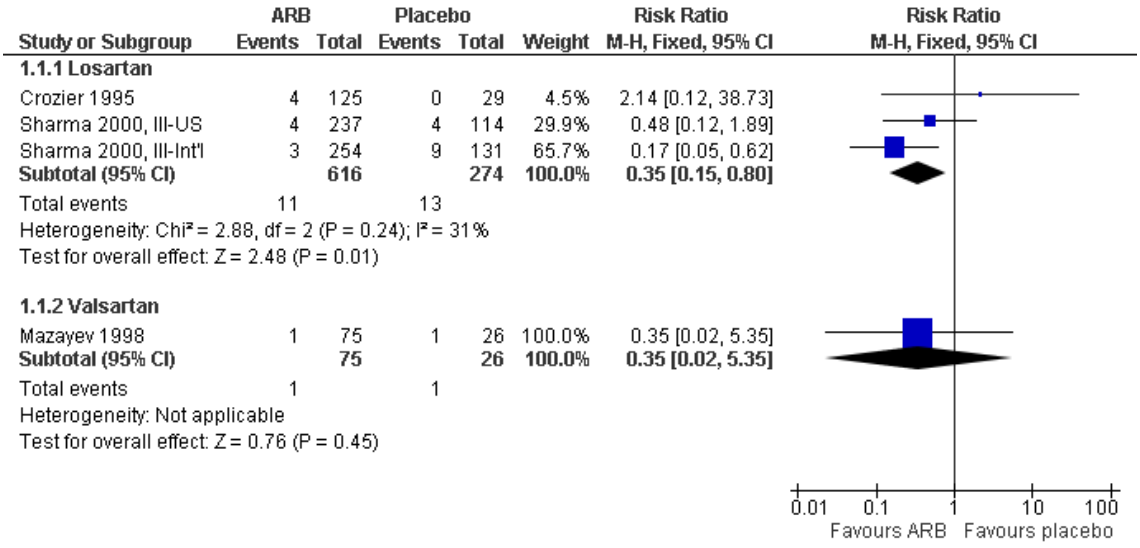

Figure 2: Pooled Result for Withdrawals Due To Adverse Effects (Obtained from Data in Reference *2*)

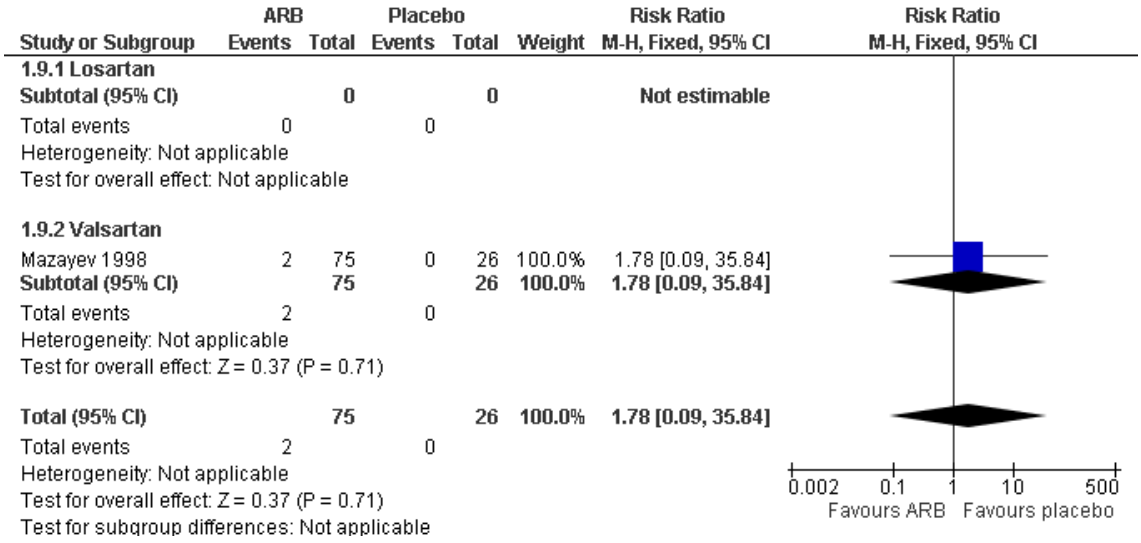

Table 1. Grade Evaluation of Clinical Outcomes – Losartan and Valsartan in Patients with Heart Failure (Assessment from Data in Reference *2*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
4 (991)	All-cause mortality	Losartan Valsartan	4	0	0	-2	-1	Very Low	Data available from indirect evidence, no RCTs comparing losartan and valsartan head to head. Limited sample sizes resulting in wide confidence intervals

Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion

8. Special Considerations and Additional Comments (*10-19*)

8.1 Regulatory Status of the Product in National Regulatory Authorities (NRAs)

The following table reflects the regulatory status of the product (innovator and generic – if applicable) in the 7 PAHO Region Reference NRAs (Argentina, Brazil, Canada, Colombia, Cuba, Mexico and United States) and the European Medicine Agency.

NRA	Status					
	25 mg Tab		50 mg Tab		100 mg Tab	
	Innovator	Generic	Innovator	Generic	Innovator	Generic
Argentina (ANMAT)	---	x	x	x	x	x
Brazil (ANVISA)	---	x	x	x	x	x
Canada (Health Canada)	x	x	x	x	x	x
Colombia (INVIMA)	---	x	x	x	x	x
Cuba (CECMED)	---	---	---	x	---	---
Mexico (COFEPRIS)	---	x	x	x	x	x
USA (FDA)	x	x	x	x	x	x
Europe (EMA)	x	---	x	---	x	---

8.2 PAHO Member State Prices

Through ECONMED (an electronic listserv for public officials from the health sector), PAHO requested the price paid for procurement of losartan from Member States who utilize this products in their National Public Health Programs. Unfortunately, no data has been provided to PAHO by countries in Latin America and the Caribbean. PAHO will increase efforts to obtain some prices from Member States and will distribute the information when the committee convenes in Washington, D.C.

8.3 Results of PAHO Expression of Interest

For a medicine to be eligible for inclusion in the PAHO Strategic Fund medicine list, it must have supporting evidence of safety, efficacy, and clinical effectiveness. Additionally the product must satisfy one of the following criteria as related to the pharmaceutical market:

1. The acquisition of the medicines is subject to particular challenges related to product procurement, pricing, patent status, forecasting of future needs, and exclusivity contracts between pharmaceutical companies that restrict marketing in specific geographical areas.
2. Leveraging economies of scale (increases in the volume of medicine procured) can result in lower costs.

PAHO has established this criteria to ensure the inclusion of the product in the Strategic Fund will provide value added to Member States who procure this product through PAHO.

To evaluate these pharmaceutical market factors, the Procurement (PRO) Unit of PAHO conducted an Expression of Interest (EoI) to gather information related to the product. PRO contacted 19 suppliers, which are included in the PAHO approved supplier list, and asked for product data (i.e. available presentations, manufacturing origin & capacity, potential restrictions, prices, and available technical documents).

Limited response was obtained from the contacted suppliers; however, PRO believes losartan, does meet the pharmaceutical market criteria. Nonetheless, significant challenges are present and the following are key recommendations:

- Consolidate regional demand to leverage the benefits of economies of scale. If PAHO is able to obtain sufficient demand perform an international tender and establish Long Term Agreements with suppliers.
- Increase number of PAHO approved suppliers offering this product in order to ensure availability and create a more competitive market.

8.4 Potential Value Added for Procurement of the Medicine through the Strategic Fund

The current version of the Strategic Fund medicine list, may limit treatment options of hypertension and heart failure, as the Fund does not offer any ARAs. If the presented evidence demonstrates adequate safety, efficacy, and clinical effectiveness, PAHO believes the inclusion of this product would provide Member States with an alternative pharmacological class to reduce the burden of cardiovascular disease.

Losartan is not an expensive ARA (reference price of US$ 0. 0.0172 per unit in 2011); however, PAHO would aim to consolidate regional demand to lower the costs of the product, thus easing the financial burden on Member States.

9. Search Strategy and References Supporting Intervention and Summary of Evidence

The interventions and evidence summaries presented in the three separate tables above in *Section VII.a-c* where all conducted with the same search strategy; however, each table yielded different results (selection criteria and the search strategy results). These differences are identified below is the table titled *Differences in the Selection Criteria and Search Results for each Clinical Question*. Additionally, the corresponding references for each clinical question are presented.

9.1 Inclusion Criteria

The aim of this evidence summary is to gather information from a systematic review about the benefits and risk of a drug in a specific health problem. For this reason we include in the summary the results from a rigorous systematic review, prioritizing Cochrane reviews. When a Cochrane review is not available or it is not suitable to respond the scope of the clinical question, we consider the inclusion of a systematic review that at least: i) includes a clearly defined inclusion criteria; ii) reports a recent search in at least two databases; and iii) reports any efforts from authors to assess the risk of bias from the included studies.

These criteria are the minimum requirements established by the Centre for Reviews and Dissemination to include a systematic review in the Database of Abstracts of Reviews of Effects (DARE; www.crd.york.ac.uk/crdweb/AboutPage.asp). For the specific purposes of the "Cost studies" section we include the results from an economic evaluation, that is; a comparison of two or more interventions or care alternatives (including cost-benefit analyses, cost-utility analyses, and cost-effectiveness analyses).

9.2 Search for Studies

The inclusion criteria described above determines the search for the studies planned. We design specific search algorithms to search the AHRQ Effective Health Care Program and The Cochrane Library as the main source to retrieve high quality systematic reviews. Each search in these two resources is complemented with a search in MEDLINE (accessed through PubMed) with the purpose of check any additional or more recent systematic review. The search is performed without any limitation, with the exception of PubMed in which we limit the search to the validated subset of systematic reviews (systematic[sb]). As we included only economic evaluations in the "Cost studies" section we limit the search to the NHS EED Database. In those cases that the NHS EED Database does not provide relevant results, we perform a specific search in MEDLINE, limiting the search algorithm designed to retrieve systematic review with the term cost*[tiab]. The search to develop the present clinical question was performed in May 2013, with the search strategies detailed below (Section 9.4).

9.3 Rating the Quality of the Evidence

Each evidence summary provides a rating of the quality of evidence following the GRADE guidance. GRADE specifies four categories (high, moderate, low, and very low) that are applied to the body of evidence that supports each assessed outcome. In the context of a synthesis of the evidence the quality of evidence reflects the confidence that the estimates of the effect are correct. For each clinical question one experienced researcher collects in a table the number of studies and patients included in these studies that set the body of evidence for each specific outcome discussed in the "Benefits" and "Risks" sections. The quality of evidence is then rated for each specific outcome and a final category is provided, commenting the main limitations that compromise the quality of evidence. All the information collected in the table, and the details required to the rating of the quality of evidence are obtained from the assessed systematic review used to develop the evidence summary.

9.4 Selection Criteria

One experienced researcher screens the results from the search applying the inclusion criteria commented above. If a Cochrane review is identified, it is selected to develop the evidence summary. When a Cochrane review is not suitable to respond to the scope of the formulated clinical question, the references from MEDLINE are screened.

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
What is the compared efficacy and safety of losartan versus valsartan in adult hypertension treatment?	For the purposes of this clinical question, no Cochrane reviews were available and from the 34 references obtained in MEDLINE only the assessed systematic review (*1*) fulfilled with the inclusion criteria mentioned above. We obtained indirect data about adverse effects from a Cochrane review assessing angiotensin receptor blockers for primary hypertension (*3*).	**Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ losartan 15 hits losartan 15 hits Agency for Healthcare Research and Quality – Effective Health Care Program. Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease. Number 18. AHRQ Pub. No. 10-EHC002-1. October 2009 Agency for Healthcare Research and Quality – Effective Health Care Program. Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension: An Update. Comparative Effectiveness Review. Number 34. AHRQ Pub. No. 11-EHC063-1. June 2011 [Note: both reports compares ACE inhibitors with calcium channel blockers, NO direct comparisons between losartan and valsartan] **Cochrane Database of Systematic Reviews : Issue 4 of 12, April 2013** losartan AND hypertens*:ti,ab,kw 738 hits **MEDLINE (accessed via PubMed)** valsartan[tiab] AND losartan[tiab] AND systematic[sb] 34 hits **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (losartan):TI IN NHSEED 12 hits

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
What is the compared efficacy and safety of losartan versus valsartan in adult hypertension associated with type 2 diabetes with proteinuria?	For the purposes of this clinical question, no systematic reviews were available. Thus inclusion criteria focused in phase III randomized controlled trials, with blinding, including clinical outcomes, with a minimum duration of 4 weeks, and published in peer review journals. A search in the Cochrane Central Register of Controlled Trials and MEDLINE retrieved 24 references for clinical trials. The revision of their title and abstracts led to the exclusion of 18 references. We reviewed in detail 6 publications that resulted in the exclusion of 2 reviews that did not include direct comparisons of losartan and valsartan (*2*,*3*), one trial comparing losartan versus placebo (*4*), one trial that did not assessed clinical outcomes (*5*), and the protocol for a clinical trial (*6*).	**Cochrane Central Register of Controlled Trials (The Cochrane Library; Issue 5 of 12, May 2013)** #1 losartan — 1312 hits #2 valsartan — 732 hits #3 #1 and #2 — 121 hits #4 diabet*:ti,ab — 24108 hits #5 proteinuria:ti,ab — 1397 hits #6 #4 or #5 — 25095 hits #5 #3 and #6 — 23 (7 in Clinical Trials) hits **MEDLINE (accessed via PubMed)** #19 losartan[tiab] — 6534 hits #20 valsartan[tiab] — 1989 hits #21 #19 AND #20 — 308 hits #22 diabet*[ti] — 223036 hits #23 proteinuria[ti] — 4766 hits #24 #22 OR #23 — 227286 hits #25 #21 AND #24 — 18 hits

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
What is the compared efficacy and safety of losartan versus valsartan in adult heart failure treatment?	For the purposes of this clinical question, we did not obtained head to head comparison of the interventions of interest in a specific search in Cochrane Central Register of Controlled Trials and MEDLINE. For this reason the data the data from trials comparing the drugs versus placebo contained in a Cochrane review (*2*) was used.	**The Cochrane Library; Issue 5 of 12, May 2013 (all databases)** (angiotensin receptor blocker* AND heart failure):ti, ab, kw 350 **Cochrane Central Register of Controlled Trials (The Cochrane Library; Issue 5 of 12, May 2013)** #1 losartan 1312 hits #2 valsartan 732 hits #3 #1 and #2 121 hits #4 MeSH descriptor: [Heart Failure] explode all trees 5033 hits #5 heart failure:ti 5658 hits #6 congestive cardiac failure:ti 758 hits #7 CHF:ti 124 hits #8 CCF:ti 3 hits #9 #4 or #5 or #6 or #7 or #8 6888 hits #10 #3 and #9 9 hits **MEDLINE (accessed via PubMed)** #1 losartan[tw] 7584 hits #2 valsartan[tw] 2246 hits #3 #1 and #2 379 hits #4 "Heart Failure"[MeSH] 80963 hits #5 heart failure[ti] 42876 hits #6 congestive cardiac failure[ti] 281 hits #7 CHF[ti] 440 hits #8 CCF[ti] 48 hits #9 #4 or #5 or #6 or #7 or #8 87492 hits #10 #3 and #9 48 hits

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10. Additional References

The following references are those cited in Section 2 (Public Health Relevance), Section 4 (Medicine Characteristics and Pharmacological Information) and Section 8 (Special Considerations and Additional Comments). References supporting the intervention and summary of evidence are available in Sections 9.5 - 9.7.

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Annex 5

Review of the Available Evidence of Mycophenolate Mofetil 250mg and 500mg Solid Oral Dosage Form for Potential Inclusion in the Pan American Health Organization Strategic Fund Medicine List

Annex 5: Table of Contents

1. Introduction to the PAHO Strategic Fund

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (Strategic Fund) was created by the Director of the Pan American Health Organization (PAHO) at the request of Member States of the Organization, in September 1998 during the 35th session of the Pan American Sanitary Conference.

The Strategic Fund is a regional mechanism which aims to strengthen the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe and effective supplies at affordable prices obtained by leveraging the advantages of economies of scale.

To accomplish this objective the Strategic Fund publishes a list of medicines available for procurement in name of the Organization's Member States. The list utilizes as a foundation the World Health Organization (WHO) Essential Medicines List (EML); however, recently there has been a significant increase in Member State requests to procure products not included in the WHO EML.

In order to meet the needs of PAHO Member States the PAHO Director has created an external Expert Committee to review requests for inclusion of medicines not included in the WHO EML. This Expert Committee will allow PAHO to implement a decision making mechanism in agreement with concepts of quality, efficacy, safety and when available, information related to the value they provide in relation to their cost.

The committee will work exclusively on requests to update the SF medicine list, which will enable PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this EC should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

2. Public Health Relevance (*1-3*)

2.1 Organ Transplantation Situation Worldwide

Based on the WHO definition, transplantation refers to the transfer of human cells, tissues or organs from a donor to a recipient with the aim of restoring function in the body. Organ transplantation often times represents the last recourse treatment for patients with end stage diseases and organ failures. Transplantation is often the best alternative in terms of quality of life for the patient and cost effectiveness.

The WHO Global Observatory on Donation and Transplantation (GODT), a global database collecting transplantation data from Member States, states the 2008 analyzed data from 104 countries worldwide shows around 100,800 solid organ transplant are performed every year worldwide among which 69,400 are kidney transplants (46% from living donors), 20,200 liver transplants (14.6% from living donors), 5,400 heart transplants, 3,400 lung transplants and 2,400 pancreas transplants. Europe and the region of the Americas account for the majority of the countries with donation and transplantation programs.

Along with donation programs, transplantations have to be supported by a complex pharmacotherapy in order to prevent graft rejection and ensure the patient's survival. Access to an effective and safe immunosuppressive therapy is crucial in order to reach these important outcomes. However, in low-and-middle income countries access to effective medicine can sometimes constitute a real challenge and can compromise the overall survival of the transplanted population.

2.2 Organ Transplantation in the Americas

In 2011, the Global Observatory on Donation and Transplantation (GODT) stated 10,922 kidney transplants, 2,377 liver transplants, 425 heart transplants, 271 pancreas transplants, 110 lung transplants, and 9 small bowel transplants were performed in 18 countries from Latin America, which account for approximately 566.3 million habitants. Although not all countries from the Region have set up a national registry for organ transplantation, the trend illustrates the Region of the Americas, including the United States, is a leader in solid organ transplantation with the highest rates of heart, liver and kidney transplants in the world.

Low and middle-income countries includes the majority of the vulnerable populations among which some diseases progress very rapidly and eventually lead to end stage chronic kidney failure, cirrhosis, chronic hepatitis, end stage heart failure, etc. In such cases, transplantation becomes the last life-saving alternative. However, when undergoing transplantation, patients require an effective and safe pharmacotherapy to avoid graft rejection or graft loss, prevent further complications and ensure a good quality of life. Hence, immunosuppressive therapies are critical and access to a quality medicine is essential to support the donation and transplantation process and to ensure patients can benefit from it.

3. Entity Supporting the Application and Requested Indications

3.1 Entity Supporting Application

The PAHO Blood Transfusion and Organ Transplants Advisor from the Medicines and Health Technologies Unit (HSS/MT) is requesting and supporting this application.

3.2 Requested Indications

Mycophenolate mofetil, an antimetabolite immunosuppressant, has been requested for the prophylaxis of organ rejection in adult patients receiving allogeneic renal, cardiac or hepatic transplants.

4. Medicine Characteristics and Pharmacological Information (*4-11*)

4.1 General Information

Medicine name (INN)	Mycophenolate mofetil
ATC (anatomical therapeutic chemical- WHO Drug classification system)	L04AA06
Reference trade name: (1. Innovator & 2. Generic - when available some examples provided)	Innovator: Cellcept 250mg ; 500mg (Hoffman La Roche) Generic: Mycophenolate mofetil 250mg; 500mg (Mylan) Mycophenolate mofetil 250mg;500mg (Apotex)
Therapeutic class (according to classification in the WHO EML)	Immunosuppressants - antimetabolite

4.2 Mechanism of Action

MMF undergoes rapid absorption and metabolism to form MPA (mycophenolic acid), its active metabolite, responsible for the inhibition of lymphocyte B and T proliferation. MPA is a potent, selective, uncompetitive and reversible inhibitor to inosine monophosphate dehydrogenase (IMPDh), thus inhibiting the guanosine nucleotide (purine) synthesis without incorporation into the DNA. The cytostatic effect it has on lymphocytes is primarily due to the fact that B and T lymphocytes depend on purine synthesis for proliferation. MPA is also responsible for suppressing B-lymphocytes antibody formation. Moreover, MPA does not have a direct effect on the production of interleukin-1 (IL-1) or interleukin-2 (IL-2) but is responsible in blocking the coupling of these cytokines and DNA synthesis and proliferation.

4.3 Pharmacokinetic/Pharmacodynamics Considerations

- *Absorption:*
  - Following IV and oral administration, MMF undergoes rapid and complete absorption and metabolism to its active metabolite, MPA. Oral and IV administration resulted in similar plasma levels. The mean bioavailability of orally administration MMF was 94% relative to IV administration, based on MPA AUC. Food had no effect on the extend of absorption, MPA AUC, although Cmax was decreased by 40%.
- *Distribution:*
  - Vd=3.6L/kg (IV), 4L/kg (PO); plasma albumin binding (97%, MPA), (82%, phenolic glucuronide of MPA [MPAG]).
- *Metabolism:*
  - MMF is metabolized to MPA, the active metabolite after absorption. MPA is the metabolized principally by glucuronyl transferases to form the pharmacologically inactive phenolic glucuronide of MPA (MPAG). In vivo, MPAG is then converted to free MPA via enterohepatic recirculation.
- *Excretion:*
  - Less than 1% of the drug is excreted as MPA in the urine. 93% of the initial administered dose of MMF is recovered in urine and 6% in feces. The major metabolite excreted if MPAG, which represents 87% of the oral MMF dose. Mean half-lives are: T1/2=17.9 hrs (PO), 16.6 hrs (IV).

4.4 Use in Special Populations

- *Pregnant Women (embryo fetal toxicity, pregnancy exposure prevention and planning, contraception):*
  - Category D. Teratology studies have demonstrated mycophenolate mofetil can lead to fetal toxicity and malformations. Children previously exposed to the drug during the first semester of pregnancy reported congenital malformations of heart, eye, face, ear and others. MMF is contraindicated during pregnancy unless the benefit justifies the risk to the fetus. It is recommended that MMF should not be initiated prior to a negative pregnancy test obtained one week prior to begin therapy. Two effective measures of contraception should be initiated before therapy and be pursued during therapy and up to 6 weeks after discontinuation. They should be used simultaneously unless abstinence is the preferred contraceptive method.
- *Nursing Women:*
  - It remains unknown if mycophenolate mofetil is excreted in human milk. Avoid use in nursing unless the benefits outweigh the risks taking into account the importance of the medicine for the mother.

- *Pediatrics (2 years to 18 years):*
  - Efficacy and safety in children receiving allogeneic cardiac or hepatic transplants have not been established. Moreover, safety and efficacy data for children under 2 years old is insufficient.
- *Geriatric:*
  - Caution as elderly patients may have higher incidence of adverse events and infections due to immunosuppression. The dose should consider decreased metabolism and eliminations process in the elderly and the risk higher risk of drug interactions due to polytherapy.

4.5 Dosage, Preparation and Administration

- *Dosage:*
  - Mycophenolate mofetil therapy should be initiated as soon as possible after transplantation. Intravenous administration (IV) should be switched to oral administration as soon as the patient is able to follow oral medication.
- *Renal Transplantation:*
  - The recommended dose in renal transplant patients is 1g bid administered orally or intravenously (over a 2 hour period). Total daily dosage is 2g/day.
- *Cardiac Transplantation:*
  - The recommended dose in cardiac transplant patients is 1.5g bid administered orally or intravenously (over a 2 hour period). Total daily dosage is 3g/day.
- *Hepatic Transplantation:*
  - The recommended dose in renal transplant patients is 1.5g bid administered orally or 1g bid intravenously (over a 2 hour period). Total daily dosage is 2-3g/day.
- *Administration:*
  - MMF (capsules, tablets) should be administered orally and be taken on empty stomach (the absorption and bioavailability of MMF is not altered however the MPA Cmax was decreased in the presence of food).

4.6 Contraindications

- Mycophenolate mofetil (MMF) is contraindicated if hypersensitivity to MMF, mycophenolic acid or any component of the drug product.
- IV formulation is contraindicated if allergy to Polysorbate 80 (TWEEN).

4.7 Warnings/Precautions

- *Carcinogenesis and Mutagenesis (Lymphoma and Malignancy)*
  - The combination of multiple immunosuppressive therapies increases the risk of developing lymphomas and other malignancies, particularly of the skin. The risk is proportional to the intensity and the duration of the immunosuppression. Preventive measures such as protective clothing, sunscreen with high protection and reduced exposure to sunlight and UV are necessary to limit the risk of skin cancer. Lymphoproliferative diseases or lymphoma were reported in clinical trials.

- *Endocrine and Metabolism*
  - Avoid mycophenolate mofetil in patients with Lesch-Nyhan and Kelley-Seegmiller Syndrome rare hereditary deficiency.
- *Gastrointestinal*
  - Caution in patients with active serious digestive systems disease. Mycophenolate mofetil has been associated with an increases incidence of digestive system adverse events (ex: gastrointestinal bleeding).
- *Immune (infections, latent viral infections, neutropenia)*
  - There is an increased risk of infection, opportunistic infections, fatal infections and sepsis with higher immunosuppression. Some infections include latent viral reactivations such as hepatitis B or C or infections caused by polyomaviruses. Cases of progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy (BKVAN) have also been observed. Patient monitoring and immunosuppression reduction should be considered to avoid more serious adverse events.
  - Severe neutropenia can develop as a consequence of mycophenolate mofetil, of concomitant medications contributing to the adverse event, of viral infection or as a resulting combination of all. Following diagnosed neutropenia, the immunosuppressive therapy dosage should be reduced (or interrupted depending on the severity of the event) and the patient managed appropriately ensuring the graft is not at risk.
  - Finally, cases of pure red cell aplasia have been reported in patients under mycophenolate mofetil therapy combined with other immunosuppressants.
- *Renal*
  - In patients with severe chronic renal impairment, administration of doses higher than 1g twice daily should be avoided. The plasma AUC of MPA and MPAG were increased following single dose administration of mycophenolate mofetil in these patients compared to healthy subjects or less severe cases of renal impairment.
- *Immunization*
  - Avoid use of live vaccines during mycophenolate mofetil therapy. Note that some vaccine's efficacy can be decreased.

4.8 Side Effects

The table below includes adverse events reported from clinical trials and adverse events from post-marketing experience with mycophenolate mofetil. Adverse events retrieved from clinical trials may not necessarily reflect the ones observed in practice because of underlying conditions or concomitant use of medication. The types of adverse reactions reported during post-marketing surveillance are similar to those observed in clinical trials but in some instances also include additional adverse reactions.

Adverse Events from Clinical Trials	Adverse Events from Post-Marketing Surveillance
Main adverse reactions: ■ Diarrhea ■ Leucopenia ■ Sepsis ■ Vomiting *Malignancies (*after 1 & 3 years follow-up) ■ Lymphoproliferative disease ■ Non-melanomas skin carcinomas ■ Other types of malignancies *Opportunistic infections:* ■ Candida mucocutaneous ■ CMV viremia/syndrome (13.5%) ■ Herpes simplex *Pediatric population (12-18 y/o)* ■ Diarrhea ■ Leucopenia ■ Sepsis ■ Anemia ■ Infection *Elderly patients:* ■ At a higher risk of adverse events due to immunosuppression: infections (CMV), gastro-intestinal hemorrhage and pulmonary edema *Other adverse reactions*: ■ Pneumonia, influenza, respiratory tract infection, agitation, confusional state, convulsion, hypertonia, tachycardia, hypotension, hypertension, hepatitis, arthralgia, renal impairment, etc.	*Gastrointestinal:* ■ Cytomegalovirus colitis ■ Pancreatitis ■ Intestinal villous atrophy *Disorders related to immunosuppression (serious/rare):* ■ Meningitis ■ Endocarditis ■ Tuberculosis ■ Atypical mycobacterial infection ■ Agranulocytosis ■ Neutropenia ■ Aplastic anemia *Blood and lymphatic disorder:* ■ Pure red cell aplasia *Hypersensitivity:* ■ Anaphylactic reactions ■ Angioneurotic oedema *Congenital disorders:* ■ Ear malformations *Respiratory disorders:* ■ Fatal interstitial lung diseases and pulmonary fibrosis have been reported

4.9 Main Interactions

The table below lists interactions as defined in the product monograph.

Drug	Interaction
Acyclovir	MMF and acyclovir both compete for tubular secretions and concentrations of both drugs can increase
Antacids With Magnesium and Aluminum Hydroxides	Avoid simultaneous administration, antacids can decrease MMF absorption
Proton Pump Inhibitors (PPIs)	Use with caution Lansoprazole and pantoprazole reduced exposure to mycophenolic acid (MPA) due to increased pH (Cmax and AUC decreased). Clinical impact on organ rejection has not been established.
Cholestyramine	Avoid use Cholestyramine can impair enterohepatic recirculation

continues

Drug	Interaction
Cyclosporine	Use with caution Cyclosporine can decrease MPA availability by interfering with enterohepatic recirculation.
Ganciclovir	Monitoring required In renal impaired patients, monitor carefully both drugs as concentrations may increase due to competition for tubular secretion
Oral Contraceptives	Use with caution One study has showed a decrease of 15% of levonorgestrel hormone AUC. It is suggested to use hormonal contraceptive and barrier contraceptive methods together to avoid pregnancy
Sevelamer	Avoid simultaneous administration Sevelamer and other calcium free phosphate binders can affect MPA Cmax and AUC. Administer 2 hours after MMF
Norfloxacin and Metronidazole	MMF should not be administered with this specific combination because its AUC is reduced.
Ciprofloxacin and Amoxicillin plus Clavulanic Acid	Use with caution Clinical relevance of this interaction is still unclear. MPA exposure can be potentially decreased by these 2 antibiotics.
Rifampin	Avoid use unless benefits out weight the risks
Live Vaccines	Avoid use of live attenuated vaccines. Advise patients vaccinations may be less effective. Influenza vaccination might be of value.

4.10 Other

- *Storage:*
  - Tablets/Capsules: store at 25 ºC (acceptable between 15 ºC and 30ºC) and protect from light (for 500mg capsules)
- *Handling instructions:*
  - Mycophenolate mofetil tablets should not be crushed and capsules not opened. Avoid powder inhalation and skin contact with oral suspension or IV solution. Rinse thoroughly with soap and water if contact with skin or mucosa. Rinse eyes with plain water.
- *Precautions for disposal:*
  - Any unused product or waste material should be disposed of in accordance with local requirements.
- *Monitoring and laboratory tests:*
  - Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. In particular, MMF patients should be monitored for neutropenia.

5. Alternatives to Mycophenolate Mofetil Available in the Strategic Fund

The current version of the Strategic Fund medicine list includes azathioprine as an alternative antimetabolite immunosuppressant. Azathioprine is also listed on WHO Essential Medicine List.

The following document provides the supporting evidence regarding the comparison of mycophenolate mofetil and azathioprine in the treatment of adult kidney, liver and heart transplant. This document does not represent a therapeutic guideline for treatment of these conditions and it is not intended for such use.

6. Guidelines Including the Use of the Medicine in Relation with the Proposed Indications

Below are presented some of the available guidelines related to organ transplantation.

- The Transplantation Society: KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients - 2009 http://www.tts.org/index.php?option=com_content&view=article&id=642&Itemid=246
- National Institute for Clinical Excellence (NICE): Immunosuppressive Therapy for Renal Transplantation in Adults - 2004 http://www.nice.org.uk/nicemedia/live/11544/32940/32940.pdf

7. Intervention and Summary of Evidence

The indications specified in the clinical questions presented below are based on input from the PAHO technical unit supporting this request (HSS/MT) and three Member States. The evidence presented in this section was obtained in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb).

For mycophenolate mofetil, the intervention and summary evidence has been compiled in three tables, with the corresponding GRADE tables.

The search strategy and references supporting the intervention and summary of evidence for all three tables are available in *Section 9* of this dossier.

7.1 Mycophenolate Mofetil Compared to Azathioprine for Kidney Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of mycophenolate mofetil compared to azathioprine in the treatment of adult kidney transplant?

CONTEXT	Mycophenolate mofetil compared to azathioprine
Kidney transplantation is the treatment of choice for most patients with end-stage renal disease. In the developed world there is approximately 280 patients/million population with a functioning kidney transplant, and this numbers have increased in the last years. The transplant rate is around 30 patients/million population (*1*). Several medical treatments have been advocated to decrease the rate of transplantation failure. Azathioprine (AZA) is an inhibitor of purine synthesis and has been used as an immunosuppressant after transplantation since the early 1960s (*2,3*). Mycophenolate mofetil (MMF) is a newer agent registered for the prevention of renal transplant rejection in the United States in 1995 (*4*).	

continues

CONTEXT	Mycophenolate mofetil compared to azathioprine
The results of three trials in the early 90's showed a significant reduction in acute rejection rates with MMF when compared with AZA or placebo (*5-7*). Recently, another trial randomized renal transplant patients to AZA or MMF, in conjunction with CsA microemulsion and a steroid withdrawal regimen. No difference was observed in the incidence of acute rejection between the groups (*8*). With this data. a technology appraisal from the National Institute for Health and Clinical Excellence in the United Kingdom recommended the use of MMF as a first-line agent only in patients in whom the minimization of calcineurin inhibitor (CNIs) was necessary (*9*). Therefore, there is still an important controversy on which is the first line therapy in adults who received a kidney transplant.	

INTERVENTION	Mycophenolate mofetil compared to azathioprine
Mycophenolate mofetil does not show differences in survival compared to azathioprine. *Moderate quality evidence.*	
Mycophenolate mofetil reduces the risk of acute rejection and graft loss compared to azathioprine. *Moderate quality evidence.*	
Mycophenolate mofetil does not show differences in graft function compared to azathioprine. *Moderate quality evidence.*	
Mycophenolate mofetil increases the risk of diarrhea compared to azathioprine. *Moderate quality evidence.*	
Mycophenolate mofetil does not show differences in the risk of infection, cytomegalovirus infection, leucopenia, anemia or the rate of malignancies compared to azathioprine. *Low quality evidence.*	

Summary of evidence	
Benefits	We found a systematic review with 19 RCTs included. The included trials performed head to head comparisons of mycophenolate mofetil (MMF) with azathioprine (AZA) as immunosuppressive agents used from the time of transplantation. The pooled analysis of these trials included a variable number of studies, ranging from 4 to 17 trials. The studies enrolled a total of 3,143 patients who received a renal transplant, of which 1,368 received treatment with AZA and 1,775 received MMF. Dose of MMF ranged from 1 to 3gr/day, being 2 g/day the more frequent dose. Doses of AZA were more variable, ranging from 1 to 2 mg/kg/day and from 100 to 150 mg/day. Only one study used a dose of 50 to 75 mg/day. Follow-up ranged from one to 60 months. The trials assessed a series of events related to the transplant. The efficacy outcomes assessed by the review were acute rejection patient survival, graft loss including death and graft loss excluding death, and graft function measured either by the serum creatinine or glomerular filtration. Another outcomes considered were gastrointestinal (GI) side effects (diarrhea and vomiting), and other safety outcomes (total infection, citomegalovirus infection, leucopenia, anemia and total malignancy). Mycophenolate mofetil (MMF) and azathioprine (AZA) did not show differences in survival (10 RCT, 2,647 patients, HR 1.02, 95%CI 0.68 to 1.53). The results from the review showed a statistically significant reduction of graft loss (including death with a functioning graft) favoring the patients treated with MMF compared to those treated with AZA (11 RCT, 2,359 patients, HR 0.76, 95%CI 0.59 to 0.98). MMF compared to AZA also showed a significant reduction of the risk of acute rejection (17 RCT, 2,968 patients, RR 0.62; 95%CI 0.55 to 0.70). Graft function was measured either by the serum creatinine or glomerular filtration. No significant differences were observed between MMF y AZA groups when serum creatinine was considered as the measure of graft function, but considerable heterogeneity was detected (10 RCT; 2,176 patients; WMD 0.74 µmol/l, 95% CI: -7.48 to 8.96; I2 = 40.3%). Similarly, no significant difference between MMF y AZA groups was found in the studies reporting glomerular filtration rate (4 RCT; 870 patients; WMD 1.93, 95%CI – 1.06 to 4.92; I2 = 34.2%).

Summary of evidence	
Risks	The assessed systematic review (10) showed a significant increase in the risk of diarrhea in patients treated with MMF compared to AZA (6 RCT; 1,903 patients; RR 1.57; 95%CI 1.33 to 1.86). The risk of vomiting was significantly higher in the MMF compared to AZA (4 RCT; 1,487 patients; RR 1.27, 95%CI 1.01 to 1.61). However this result showed a considerable heterogeneity (I2 67.1%), and when the analysis was replicated using a random effect model, no difference was apparent between groups (RR 1.27; 95%CI 0.84 to 1.92, p = 0.26). The results of the review did not show differences between MMF and AZA in the risk of total infection (4 RCT, 1,148 patients; RR 1.03, 95%CI 0.87 to 1.21; I2 53.1%), cytomegalovirus infection (12 RCT; 2,252 patients; RR 1.09; 95%CI 0.83 to 1.42; I2 39.1%), leucopenia (10 RCT; 2,549 patients; RR 1.08; 95%CI 0.85 to 1.39; I2 43.9), anemia (6 RCT; 1,894 patients; RR 1.01, 95%CI 0.87 to 1.18; I2 32.1) or total malignancy (5 RCT; 1,741 patients; RR 1.17; 95%CI 0.75 to 1.81).
Comments/ Applicability	According to the review authors' point of view, if the improvement showed by the results in graft survival observed with MMF is real then there is a strong argument for the use of MMF as a first-line immunosuppressant after renal transplantation. Even if not, the reduction in the risk of acute rejection with MMF may still be advantageous in a cost benefit analysis (*10*).
	The authors also highlighted the finding of a similar safety profile of the two drugs, because one of the possible advantages of MMF would be the reduction of its systemic toxicity. However, the study showed a significantly higher incidence of diarrhea and vomiting with MMF, with no difference in risk of any of the other side effects (*10*).
	On the other hand, the applicability of these results should be considered in the light of the issues related to their validity, due to the significant heterogeneity detected in a number of analyses, the poor reporting of some important outcomes in the included studies and the poor methodological quality of the trials (*10*).
	Another issue to note is the poor quality in the methodology and reporting of the included trials. Only 2 of the 19 considered trials were regarded as good quality according to the Jadad score, with only two reporting adequate allocation concealment and six reporting an intention-to-treat analysis. On the other hand, the survival outcomes were poorly reported in the original trials, and authors had to estimate data to calculate HRs from other reported statistics, such as the number of events and the log-rank statistic, which could weaken the review conclusions.
Cost studies	A technology assessment commissioned by NICE included seven published economic evaluations (*9*). Four of these studies were cost-consequence analyses and the rest were cost-effectiveness analyses. All the evaluations included healthcare costs only. Only one of the studies included a time horizon greater than 1 year. Most cost analyses, with the exception of two, showed that the costs of mycophenolate mofetil were greater at 6 months or 1 year compared with those of azathioprine. One of the cost analyses that considered the outcomes of treatment over a longer period suggested that this cost difference was maintained at 10 years. The remaining two cost analyses estimated the short-term costs of mycophenolate mofetil to be lower than those associated with azathioprine. Two cost-effectiveness analyses estimated both the cost and the effectiveness of mycophenolate mofetil to be superior to those of azathioprine at 10 years. Another study showed an incremental cost per QALY estimate of approximately 50,000 Canadian dollars. The Assessment Group responsible of the technology assessment performed their own economic evaluation, but focused in the replacement of azathioprine with mycophenolate mofetil in a ciclosporin-based treatment regimen.

Table 1. GRADE Evaluation of Clinical Outcomes: (Mycophenolate Mofetil Compared to Azathioprine for Kidney Transplant Recipients (Assessment for all the Outcomes from Data in Reference *10*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
17 (2968)	Acute rejection	MMF AZA	4	-1	0	0	0	Moderate	Most of studies with poor methodological quality (lack of allocation concealment, no ITT analysis). Significant asymmetry in the funnel plot suggesting publication bias toward studies favoring MMF.
10 (2647)	Patient survival	MMF AZA	4	-1	0	0	0	Moderate	Most of studies with poor methodological quality (lack of allocation concealment, no ITT analysis).
11 (2359)	Graft loss	MMF AZA	4	-1	0	0	0	Moderate	Most of studies with poor methodological quality (lack of allocation concealment, no ITT analysis).
6 (1903)	Diarrhoea	MMF AZA	4	-1	0	0	0	Moderate	Most of studies with poor methodological quality (lack of allocation concealment, no ITT analysis).
4 (1487)	Vomiting (a rest of adverse effects or safety data)	MMF AZA	4	-1	-1	0	0	Low	Data available from only four studies with poor methodological quality, heterogeneity > 50%.
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

7.2 Mycophenolate Mofetil Compared to Azathioprine for Liver Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of mycophenolate mofetil compared to azathioprine in the treatment of adult liver transplant?

CONTEXT	Mycophenolate mofetil compared to azathioprine

Liver transplantation has become an established treatment option for end-stage liver failure in selected patients, which has resulted in improved survival and quality of life (*1*). Over 4,000 liver transplantations are performed annually in Europe and more than 6,000 in the USA (*2,3*). Liver transplant is performed mainly for end-stage liver failure arising as a result of chronic liver disease (for example, cirrhosis due to alcohol consumption, viruses), acutely (viruses, drug overdose), or as a result of tumours (*4*). Liver transplant recipients have a one-year survival of over 90% and a five-year survival of over 75% (*5*).

Important problems for patients undergoing liver transplantation remain, including primary non-function of the allograft and acute kidney failure requiring dialysis. The primary non-function of the allograft condition affects 7% to 19% of liver transplantation recipients. It usually requires emergency re-transplantation and increases the risk of death (*6*). Several medical treatments have been advocated to decrease the rate of transplantation failure, such as azathioprine and mycophenolate mofetil.

Azathioprine is more myelotoxic and hepatotoxic than mycophenolate mofetil, but mycophenolate mofetil is associated with a higher risk of diarrhea and vomiting. Therefore, there is still an important controversy around the fact of which is the first line therapy in adults who received a liver transplant.

INTERVENTION	Mycophenolate mofetil compared to azathioprine
Mycophenolate mofetil does not show differences in patient or graft survival compared to azathioprine. *Low quality evidence.*	
Mycophenolate mofetil reduces the risk of acute rejection compared to azathioprine. *Low quality evidence.*	
Mycophenolate mofetil reduces the risk of thrombocytopenia compared to azathioprine. *Low quality evidence.*	
Mycophenolate mofetil does not show differences in the rate of infections, gastrointestinal symptoms or leucopenia compared to azathioprine. *Low quality evidence.*	

Summary of evidence	
Benefits	We found a systematic review with 3 RCTs included (*7*). The included trials performed head to head comparisons of mycophenolate mofetil (MMF) with azathioprine (AZA), both comprised into a cyclosporine-based regimen. A total of 628 patients were included, 309 in the MMF group and 319 in the AZA group. Two trials had a small sample size (N=57 (*8*); and N=63 (*9*)), and most of patients were included in the remaining trial (N=565 (*10*)). Doses of MMF ranged from 1 to 1.5gr twice daily Doses of AZA ranged from 1 to 2 mg/kg/day. Median follow-up was from 10 months to a minimum of 12 months. A pooled analysis of the included trials results was not possible, and the review reported the results narratively. According the results of the included trials, mycophenolate mofetil (MMF) and azathioprine (AZA) did not show differences in mortality (89.3% MMF versus 85.7% AZA in one trial (*10*); 88% MMF versus 87.1% AZA in other trial (9)). Graft survival also was similar between treatments (87.5% MMF versus 81.3% AZA in one trial (10); 86.3% MMF versus 85.4% AZA in another (*9*)). In one of the included trials acute rejection was more frequent with AZA compared to MMF, but such difference failed to reach statistical significance (19.4% versus 40.6%) (*9*). However, in another trial with a larger number of participants, the patients receiving MMF had a significant reduction of acute rejection compared to AZA (38.5% versus 47.7%, p = 0.02) (*10*).

Summary of evidence	
Risks	The assessed systematic review (*7*) did not show differences in the rate of infections between MMF and AZA treated patients (32% versus 31% (*10*); 45.5% versus 43.2%, (*9*)). No significant increase in the risk of gastrointestinal symptoms was observed with MMF compared to AZA (12.9% versus 6.2% (*10*); 51.3% versus 49.8% (*9*)). In one study (N=63) (*10*) thrombocytopenia was significantly more frequent with AZA compared to MMF, and the difference reached statistical significance (19.4% MMF versus 46.9% AZA; $p < 0.05$). However, the trial with the largest sample (N=565; 9) did not show such statistically significant difference (6.9% MMF versus 12.5% AZA). The frequency of leukopenia was lower in patients that received MMF compared to AZA in a trial (6.5% versus 18.8%) (*10*), but the difference did not reach statistical significance. Another trial showed the opposite results, with more patients receiving MMF with leukopenia (3.6% versus 0.7) (*9*).
Comments/ Applicability	The results of the assessed review failed to show a significant benefit with MMF compared to AZA, except for the outcomes acute rejection and frequency of thrombocytopenia, both favouring MMF. However, these benefits were observed only in one trial each, with a limited number of participants and events. Moreover, according to author´s point of view, the same criteria for obtaining liver biopsies on the basis of suspected rejection were used in both trials, so that the evaluation of rejection in these studies cannot be considered reliable (*7*).
	Two of the included studies used cyclosporine-based immunosuppressive regimens. Authors pointed out that, as a vast majority of liver transplant programs use tacrolimus-based immunosuppression, any differences between AZA and MMF for rejection might be obviated by the use of tacrolimus (*7*).
	It is important to note the finding of a similar safety profile of the drugs studied, as one of the possible advantages of MMF would be the reduction of its systemic toxicity. Nonetheless, data should be interpreted with caution because of the small number of events in each group, so that the absence of difference in the analyses may result from a lack of statistical power, instead of an apparent similarity between the treatments.
	Another weakness of this review is the poor quality in the reporting of the included studies characteristics, which preclude from making a reliable judgment about the quality of the evidence.
	The applicability of these results is very limited due to the limited number of trials, participants and events in the analyses, and the poor reporting of important characteristics of the included studies. The results of this review suggest that the perceived clinical benefits of MMF over AZA in patients receiving a liver transplantation are not supported by good evidence. Randomized controlled studies are needed to define the first line treatment for the maintenance of immunosuppression in liver transplantation.
Cost studies	The search did not retrieve relevant economic evaluations assessing the cost-effectiveness of MMF compared to AZA in liver transplantation.

Table 1. GRADE Evaluation of Clinical Outcomes: (Mycophenolate Mofetil Compared to Azathioprine for Liver Transplant Recipients (Assessment from Data in Reference *7*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
2 (628)	Acute rejection	MMF AZA	4	-2	N/A	0	N/A	Low	Data available from only two trials, one of them unblinded, with a limited number of participants and events in each outcome.
2 (628)	Patient survival	MMF AZA	4	-2	N/A	0	N/A	Low	Data available from only two trials, one of them unblinded, with a limited number of participants and events in each outcome.
2 (628)	Graft survival	MMF AZA	4	-2	N/A	0	N/A	Low	Data available from only two trials, one of them unblinded, with a limited number of participants and events in each outcome.
2 (628)	GI symptoms	MMF AZA	4	-2	N/A	0	N/A	Low	Data available from only two trials, one of them unblinded, with a limited number of participants and events in each outcome.
2 (628)	Safety outcomes	MMF AZA	4	-2	N/A	0	N/A	Low	Data available from only two trials, one of them unblinded, with a limited number of participants and events in each outcome.
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

7.3 Mycophenolate Mofetil Compared to Azathioprine for Heart Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of mycophenolate mofetil compared to azathioprine in the treatment of adult heart transplant?

CONTEXT	Mycophenolate mofetil compared to azathioprine
Cardiac transplantation remains the definitive therapy for patients with end-stage heart disease who have exhausted other therapeutic alternatives (*1*). The development of new immunosuppressive agents has resulted in good long-term survival rates in the majority of heart transplant recipients. Adverse effects of immunosuppresses (mainly steroids and calcineurin inhibitors) are some of the limiting factors affecting patient survival and quality-of-life, aside from cardiac allograft vasculopathy and malignancy (*2*). The leading causes of death 5 years post-transplantation are cardiac allograft vasculopathy (CAV) and late graft failure (likely due to CAV), which together account for 30% of deaths, followed by malignancies (24% if deaths) and non-cytomegalovirus infections (10% of deaths) (*1*). Mycophenolate mofetil (MMF), which is rapidly hydrolyzed after ingestion to mycophenolic acid, is a selective, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase, a key enzyme in the de novo synthesis of guanine nucleotides. This functional selectivity allows lymphocyte proliferation to be specifically targeted with less anticipated effect on erythropoiesis and neutrophil production than is seen with azathioprine (*3*). MMF could be an alternative to azathioprine, due to fewer side effects on erythropoiesis and neutrophil production.	

INTERVENTION	Mycophenolate mofetil compared to azathioprine
Mycophenolate mofetil reduces the risk of death and of receiving an additional heart transplant compared to azathioprine. *Very low quality evidence.*	
Mycophenolate mofetil increases the time to death or requirement of an additional heart transplant compared to azathioprine. *Very low quality evidence.*	
Mycophenolate mofetil reduces the dose requirement of cyclosporine compared to azathioprine. *Very low quality evidence.*	
Mycophenolate mofetil increases the risk of tissue invasion by Herpes simplex and cytomegalovirus compared to azathioprine. *Very low quality evidence.*	

Summary of evidence	
Benefits	The search did not identify a systematic reviews assessing the effectiveness of mycophenolate mofetil (MMF) compared to azathioprine (AZA) in treatment of an adult with a heart transplant. A specific search of trials retrieved a double blind study in 650 patients, undergoing their first cardiac transplant at 28 heart transplant centers in Australia, Europe, and North America (*1*). Patients in this study were adults and their baseline characteristics are outlined in the table 1. Patients were enrolled and randomized in the study before transplantation, but study drug was not initiated until the patient was able to take oral medications. Patients unable to take medications orally more than 5 days after surgery were withdrawn from the study. Each center determined whether early rejection prophylaxis with antithymocyte globulin (ATG) or the murine monoclonal anti-CD3 antibody (OKT3) was used postoperatively according to standard practice at the institution. In all patients, cyclosporine was titrated to maintain a trough level reflecting the standard target assay range at each center. Methylprednisolone (500-1000 mg) was administered intravenously pre or intraoperatively.

continues

Summary of evidence	
Benefits *(cont.)*	After surgery, methylprednisolone in a dose up to 500 mg was given within 12 hours. Oral prednisolone (or an intravenous equivalent) was thereafter begun at a dose of 1 mg/kg/day and tapered to 0.3 mg/kg/day by 30 days after transplant, 0.15 mg/kg/day by 90 days after transplant, and 0.1 mg/kg/day by 180 days after transplant. Azathioprine at 4mg/kg was given preoperatively to all patients. The use medication for cytomegalovirus, Pneumocystis carinii, herpes simplex, peptic ulcer disease, and osteoporosis prophylaxis was according to standard institutional practice and was not controlled for in this study. Analysis of efficacy was based on two populations: i) all enrolled patients and ii) the subset of patients receiving at least a single dose of study medication. In total, 650 heart transplant recipients were enrolled and randomized to receive either AZA (N=323) or MMF (N=327); 578 patients received at least one dose of study medication (N=289 in each group) and were included in the treated population. In this trial, after 3 years of follow up more patients in the azathioprine group (53/289; 18.3%) compared to the mycophenolate mofetil group (34/289; 11.8%) died or received another transplant (P<0.01). Four patients (2 in each treatment group) underwent re-transplantation during the first year; 1 additional patient in the MMF group underwent re-transplantation in the third post-transplant year. Patients treated with mycophenolate mofetil had a longer time until retransplantation or patient death than patient treated with azathioprine (weighted pair-wise difference 6.54; 95%CI 1.12 to 11.97; log rank test; p=0.029). Sixty patients in the AZA group and 53 patients in the MMF group had baseline and 36-month intravascular ultrasound (IVUS studies). The change in mean maximal intimal thickness was lower for the MMF patients than for the AZA patients (0.06 +/- 0.03 mm vs 0.13 +/- 0.03mm; p=0.056). On the other hand, one year after transplantation, the mean dose of cyclosporine was 3.9mg/kg 4 times daily for the AZA group and 3.4 mg/kg 4 times daily for the MMF group (p=0.011). There was no significant difference between treatment groups in mean change in lumen diameter of all coronary artery segments on quantitative coronary angiography (QCA) at any time-point in either population (12 months: AZA 8/177, MMF 5/181; p=0.345; 24 months: AZA 9/143, MMF 6/155; p=0.282).
Risks	The included clinical trial evaluated the incidence of infection, malignancy and other adverse events as safety outcomes (*1*). Compared azathioprine, mycophenolate mofetil accounted for a greater rate of tissue invasion by Herpes simplex (AZA 46/289 (15.9%), MMF 66/289 (22.85%); p<0.05) and cytomegalovirus (AZA 25/289 (8.7%), MMF 38/289 (13.1%); p<0.05). Among patients who did not receive induction therapy, the difference regarding tissue invasion by Herpes zoster was not statistically significant. The number of patients with malignancies was similar in the AZA and MMF groups (45 (15.6%) AZA vs 36 (12.5%) MMF).
Comments/ Applicability	Some aspects from the assessed trial make the interpretation of its results and its applicability to a wider community difficult (*1*). Approximately 10% of the patients never received the study drug. When the analysis included those patients, from an intention to treat approach, there was no survival difference between MMF and AZA. Differences were only shown analysing patients that received the drug. In the other hand, there was a more than 30% dropout rate in the first year for a variety of reasons making interpretations difficult. Third, despite being the largest cardiac transplant immunosuppression trial, the numbers of patients enrolled were still rather modest with approximately 300 patients per arm. Finally, the study was limited to larger volume centers (*4*). On the other hand, the cost of MMF is four to five times higher than AZA.
	The results of the included trial (*1*) have been confirmed recently by the results of the Joint UNOS/ ISHLT thoracic registry (*4*), but additional head-to-head trials would be necessary to confirm the results available.

Summary of evidence	
Cost studies	The search did not retrieved relevant economic evaluations assessing the cost-effectiveness of MMF compared to AZA in heart transplantation. A study reported data on cost-effectiveness of everolimus and MMF versus AZA in de novo heart transplantation (*5*). The cost-effectiveness was assessed up to 6 months post transplantation. The evaluation was performed from the German health insurance payer perspective with the data of two clinical trials employed a similar design and population criteria. One year after transplant effectiveness results for MMF were obtained from the assessed trial (*1*). However, the primary efficacy endpoint in the MMF trial differed from that of the everolimus trial. Data were adjusted accordingly to express cost-effectiveness in terms of the same efficacy outcome. The incremental 6-month cost versus AZA was €2535 for everolimus and €3007 for MMF. The absolute reduction in efficacy failure versus AZA was 10.4% for everolimus and 9.8% and 10.1% for MMF, respectively. The incremental cost per efficacy failure avoided was €29.912 for MMF. In conclusion, everolimus was more cost-effective than MMF versus AZA in the first 6 months after heart transplantation.

Table 1. Characteristics Demographics in Enrolled Patients (*1*)

	AZA	MMF
Mean age +/- SD	51.1 +/- 10.1	52.4 +/- 9.4
Female (%)	48 (15)	56 (17)
Caucasian (%)	279 (86)	285 (87)
Mean weigth +/- SD (kg)	77.5 +/- 13.9	78.6 +/- 17.3
Pretransplant diagnosis CAD (%9	157 (49)	168 (52)
Pretransplant diagnosis IDC (%)	113 (35)	99 (30)
CMV mismatch (%)	51 (16)	50 (15)
Mean donor age +/-SD (yr)	31.2 +/- 13.2	30.1 +/- 12.7

Table 2. GRADE Evaluation of Clinical Outcomes: (Mycophenolate Mofetil Compared to Azathioprine for Heart Transplant Recipients (Assessment from Data in Reference *1*)

Number of Studies (N)	Variable	Comparison	Type of Evidence	Quality	Inconsistency	Indirectness	Imprecision	GRADE	Comments
1 (578)	Period of time to received another transplant	Azathioprine Mycophenolate mofetil	4	-2	0	0	-1	Very Low	Intention to treat was not clear (approximately 10% of the patients never received the study drug). There was a more than 30% dropout rate during the first year Small size sample
1 (650)	Time to re-transplantation or patient death	Azathioprine Mycophenolate mofetil	4	-2	0	0	-1	Very Low	Idem
1 (650)	Change in mean maximal intimal thickness	Azathioprine Mycophenolate mofetil	4	-2	0	0	-1	Very Low	Idem
1 (650)	Change in lumen diameter of all coronary artery segments on quantitative coronary angiography	Azathioprine Mycophenolate mofetil	4	-2	0	0	-1	Very Low	Idem
1 (650)	Cardiac function	Azathioprine Mycophenolate mofetil	4	-2	0	0	-1	Very Low	Idem
1 (650)	Infections	Azathioprine Mycophenolate mofetil	4	-2	0	0	-1	Very Low	Idem
1 (650)	Malignancies	Azathioprine Mycophenolate mofetil	4	-2	0	0	-1	Very Low	Idem
Type of evidence: 4 = ECA; 2 = Observational studies; 1 = Non-analytic studies / Expert opinion									

8. Special Considerations and Additional Comments (*12-21*)

8.1 Regulatory Status of the Product In National Regulatory Authorities (NRAs)

The following table reflects the regulatory status of the product (innovator and generic – if applicable) in the 7 PAHO Region Reference NRAs (Argentina, Brazil, Canada, Colombia, Cuba, Mexico and United States) and the European Medicine Agency.

NRA	Status			
	250 mg Cap		500 mg Cap/Tab	
	Innovator	Generic	Innovator	Generic
Argentina (ANMAT)	x	x	x	x
Brazil (ANVISA)	---	---	x	x
Canada (Health Canada)	x	x	x	x
Colombia (INVIMA)	x	x	x	x
Cuba (CECMED)	x	x	x	x
Mexico (COFEPRIS)	---	---	---	---
USA (FDA)	x	x	x	x
Europe (EMA)	x	x	x	x

8.2 PAHO Member State Prices

Through ECONMED (an electronic listserv for public officials from the health sector), PAHO requested the price paid for procurement of mycophenolate mofetil from Member States who utilize this products in their National Public Health Programs. Unfortunately, no data has been provided to PAHO by countries in Latin America and the Caribbean. PAHO will increase efforts to obtain some prices from Member States and will distribute the information when the committee convenes in Washington, D.C.

8.3 Results of PAHO Expression of Interest

For a medicine to be eligible for inclusion in the PAHO Strategic Fund medicine list, it must have supporting evidence of safety, efficacy, and clinical effectiveness. Additionally the product must satisfy one of the following criteria as related to the pharmaceutical market:

1. The acquisition of the medicines is subject to particular challenges related to product procurement, pricing, patent status, forecasting of future needs, and exclusivity contracts between pharmaceutical companies that restrict marketing in specific geographical areas.
2. Leveraging economies of scale (increases in the volume of medicine procured) can result in lower costs.

PAHO has established this criteria to ensure the inclusion of the product in the Strategic Fund will provide value added to Member States who procure this product through PAHO.

To evaluate these pharmaceutical market factors, the Procurement (PRO) Unit of PAHO conducted an Expression of Interest (EoI) to gather information related to the product. PRO contacted 19 suppliers, which are included in the PAHO approved supplier list, and asked for product data (i.e. available presentations, manufacturing origin & capacity, potential restrictions, prices, and available technical documents).

Limited response was obtained from the contacted suppliers; however, PRO believes mycophenolate mofetil, does meet the pharmaceutical market criteria. Nonetheless, significant challenges are present and the following are key recommendations:

- Consolidate regional demand to leverage the benefits of economies of scale. If PAHO is able to obtain sufficient demand perform an international tender and establish Long Term Agreements with suppliers.
- Increase number of PAHO approved suppliers offering this product in order to ensure availability and create a more competitive market.

8.4 Potential Value Added for Procurement of the Medicine through the Strategic Fund

The current version of the Strategic Fund medicine list, published in April of 2013, may limit options in treatment of patients receiving transplants, as the Fund offers two immunosuppressive medicines (azathioprine & cyclosporine) and of these two, only azathioprine is an antimetabolite immunosuppressant. If the presented evidence demonstrates adequate safety, efficacy, and clinical effectiveness, PAHO believes the inclusion of this product will improve Member States access to an effective and safe medicine that can be used to improve graft and patient survival in post-transplant therapy.

In comparison to azathioprine, mycophenolate mofetil is more expensive. For example, 2011 reference prices indicate mycophenolate mofetil 250 mg (US$ 1.0335 per unit) cost ~4 times more than azathioprine 50 mg (US$ 0.2774 per unit). If included in the Strategic Fund List, PAHO would aim to consolidate regional demand to lower the costs of the product, thus easing the financial burden on Member States.

9. Search Strategy and References Supporting Intervention and Summary of Evidence

The interventions and summary of evidences presented in the three separate tables above in *Section VII.a-c* where all conducted with the same search strategy; however, each table yielded different results (selection criteria and the search strategy results). These differences are identified below is the table titled *Differences in the Selection Criteria and Search Results for each Clinical Question*. Additionally, the corresponding references for each clinical question are presented.

9.1 Inclusion Criteria

The aim of this evidence summary is to gather information from a systematic review about the benefits and risk of a drug in a specific health problem. For this reason we include in the summary the results from a rigorous systematic review, prioritizing Cochrane reviews. When a Cochrane review is not available or it is not suitable to respond the scope of the clinical question, we consider the inclusion of a systematic review that at least: i) includes a clearly defined inclusion criteria; ii) reports a recent search in at least two databases; and iii) reports any efforts from authors to assess the risk of bias from the included studies.

These criteria are the minimum requirements established by the Centre for Reviews and Dissemination to include a systematic review in the Database of Abstracts of Reviews of Effects (DARE; www.crd.york.ac.uk/crdweb/AboutPage.asp). For the specific purposes of the "Cost studies" section we include the results from an economic evaluation, that is; a comparison of two or more interventions or care alternatives (including cost-benefit analyses, cost-utility analyses, and cost-effectiveness analyses).

9.2 Search for Studies

The inclusion criteria described above determines the search for the studies planned. We design specific search algorithms to search the AHRQ Effective Health Care Program and The Cochrane Library as the main source to retrieve high quality systematic reviews. Each search in these two resources is complemented with a search in MEDLINE (accessed through PubMed) with the purpose of check any additional or more recent systematic review. The search is performed without any limitation, with the exception of PubMed in which we limit the search to the validated subset of systematic reviews (systematic[sb]). As we included only economic evaluations in the "Cost studies" section we limit the search to the NHS EED Database. In those cases that the NHS EED Database does not provide relevant results, we perform a specific search in MEDLINE, limiting the search algorithm designed to retrieve systematic review with the term cost*[tiab]. The search to develop the present clinical question was performed in May 2013, with the search strategies detailed below (Section 9.4).

9.3 Rating the Quality of the Evidence

Each evidence summary provides a rating of the quality of evidence following the GRADE guidance. GRADE specifies four categories (high, moderate, low, and very low) that are applied to the body of evidence that supports each assessed outcome. In the context of a synthesis of the evidence the quality of evidence reflects the confidence that the estimates of the effect are correct. For each clinical question one experienced researcher collects in a table the number of studies and patients included in these studies that set the body of evidence for each specific outcome discussed in the "Benefits" and "Risks" sections. The quality of evidence is then rated for each specific outcome and a final category is provided, commenting the main limitations that compromise the quality of evidence. All the information collected in the table, and the details required to the rating of the quality of evidence are obtained from the assessed systematic review used to develop the evidence summary.

9.4 Selection Criteria

One experienced researcher screens the results from the search applying the inclusion criteria commented above. If a Cochrane review is identified, it is selected to develop the evidence summary. When a Cochrane review is not suitable to respond to the scope of the formulated clinical question, the references from MEDLINE are screened.

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
What is the efficacy and safety of mycophenolate mofetil compared to azathioprine in the treatment of adult kidney transplant?	For the purposes of this clinical question, no Cochrane reviews were available and from the 41 references obtained in MEDLINE only the assessed systematic review (*10*) fulfilled with the inclusion criteria mentioned above.	**Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ transplantation 24 hits immunosuppress* 8 hits mycophenolate mofetil 3 hits **Cochrane Database of Systematic Reviews: (The Cochrane Library; Issue 4 of 12, April 2013)** transplantat* AND immunosuppress* 365 hits transplantat* AND mycophenolate mofetil 216 hits **MEDLINE (accessed via PubMed)** 1 transplantat*[ti] AND mycophenolate[tiab] AND systematic[sb] 35 hits 2 azathioprine[ti] AND mycophenolate[tiab] AND systematic[sb] 8 hits 3 1 OR 2 41 hits **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (mycophenolate AND azathioprine): TI IN NHSEED 0 hits
What is the efficacy and safety of mycophenolate mofetil compared to azathioprine in the treatment of adult liver transplant?	For the purposes of this clinical question, no Cochrane reviews were available and from the 47 references obtained in MEDLINE only the assessed systematic review (*7*) fulfilled with the inclusion criteria mentioned above.	**Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ transplantation 24 hits immunosuppress* 8 hits mycophenolate mofetil 3 hits **Cochrane Database of Systematic Reviews: (The Cochrane Library; Issue 4 of 12, April 2013)** transplantat* AND immunosuppress* 365 hits transplantat* AND mycophenolate mofetil 216 hits **MEDLINE (accessed via PubMed)** transplantat*[ti] AND mycophenolate[tiab] AND systematic[sb] 35 hits azathioprine[ti] AND mycophenolate[tiab] AND systematic[sb] 8 hits azathioprine[ti] AND mycophenolate[tiab] AND liver[ti] 5 hits **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (mycophenolate AND azathioprine): TI IN NHSEED 0 hits

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
What is the efficacy and safety of mycophenolate mofetil compared to azathioprine in the treatment of adult heart transplant?	For the purposes of this clinical question, no systematic reviews were available. A search in the Cochrane Central Register of Controlled Trials retrieved 20 references for clinical trials. The revision of their title and abstracts led to the exclusion of 16 references. We reviewed in detail 4 publications that resulted in the exclusion of an economic evaluation of everolimus and mycophenolate mofetil assessed in the "Cost studies" section of this clinical question (*5*), the report of the results from a clinical registry (*6*), and the short terms results report from the included clinical trial (*7*).	**Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ transplantation 24 hits immunosuppress* 8 hits mycophenolate mofetil 3 hits **Cochrane Database of Systematic Reviews: (The Cochrane Library; Issue 4 of 12, April 2013)** transplantat* AND immunosuppress* 365 hits transplantat* AND mycophenolate mofetil 216 hits **Cochrane Central Register of Controlled Trials : Issue 5 of 12, May 2013** Mycophenolate:ti,ab AND azathioprine:ti,ab AND (heart OR cardiac):ti 20 hits **MEDLINE (accessed via PubMed)** transplantat*[ti] AND mycophenolate[tiab] AND systematic[sb] 35 hits azathioprine[ti] AND mycophenolate[tiab] AND systematic[sb] 8 hits azathioprine[ti] AND mycophenolate[ti] AND (heart[ti] OR cardiac[ti]) 7 hits **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (mycophenolate AND azathioprine):TI IN NHSEED 0 hits

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10. Additional References

The following references are those cited in Section 2 (Public Health Relevance), Section 4 (Medicine Characteristics and Pharmacological Information) and Section 8 (Special Considerations and Additional Comments). References supporting the intervention and summary of evidence are available in Sections 9.5 - 9.7.

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Annex 6

Review of the Available Evidence of Sirolimus Tablet (0.5, 1 & 2mg) and Oral Solution (1mg/ml) for Potential Inclusion in the Pan American Health Organization Strategic Fund Medicine List

Annex 6: Table of Contents

1. Introduction to the PAHO Strategic Fund

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (Strategic Fund) was created by the Director of the Pan American Health Organization (PAHO) at the request of Member States of the Organization, in September 1998 during the 35th session of the Pan American Sanitary Conference.

The Strategic Fund is a regional mechanism which aims to strengthen the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe and effective supplies at affordable prices obtained by leveraging the advantages of economies of scale.

To accomplish this objective the Strategic Fund publishes a list of medicines available for procurement in name of the Organization's Member States. The list utilizes as a foundation the World Health Organization (WHO) Essential Medicines List (EML); however, recently there has been a significant increase in Member State requests to procure products not included in the WHO EML.

In order to meet the needs of PAHO Member States the PAHO Director has created an external Expert Committee to review requests for inclusion of medicines not included in the WHO EML. This Expert Committee will allow PAHO to implement a decision making mechanism in agreement with concepts of quality, efficacy, safety and when available, information related to the value they provide in relation to their cost.

The committee will work exclusively on requests to update the SF medicine list, which will enable PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this EC should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

2. Public Health Relevance (*1-3*)

2.1 Organ Transplantation Situation Worldwide

Based on the WHO definition, transplantation refers to the transfer of human cells, tissues or organs from a donor to a recipient with the aim of restoring function in the body. Organ transplantation often times represents the last recourse treatment for patients with end stage diseases and organ failures. Transplantation is often the best alternative in terms of quality of life for the patient and cost effectiveness.

The WHO Global Observatory on Donation and Transplantation (GODT), a global database collecting transplantation data from Member States, states the 2008 analyzed data from 104 countries worldwide shows around 100,800 solid organ transplant are performed every year worldwide among which 69,400 are kidney transplants (46% from living donors), 20,200 liver transplants (14.6% from living donors), 5,400 heart transplants, 3,400 lung transplants and 2,400 pancreas transplants. Europe and the region of the Americas account for the majority of the countries with donation and transplantation programs.

Along with donation programs, transplantations have to be supported by a complex pharmacotherapy in order to prevent graft rejection and ensure the patient's survival. Access to an effective and safe immunosuppressive therapy is crucial in order to reach these important outcomes. However, in low-and-middle income countries access to effective medicine can sometimes constitute a real challenge and can compromise the overall survival of the transplanted population.

2.2 Organ Transplantation in the Americas

In 2011, the Global Observatory on Donation and Transplantation (GODT) stated 10,922 kidney transplants, 2,377 liver transplants, 425 heart transplants, 271 pancreas transplants, 110 lung transplants, and 9 small bowel transplants were performed in 18 countries from Latin America, which account for approximately 566.3 million habitants. Although not all countries from the Region have set up a national registry for organ transplantation, the trend illustrates the Region of the Americas, including the United States, is a leader in solid organ transplantation with the highest rates of heart, liver and kidney transplants in the world.

Low and middle-income countries includes the majority of the vulnerable populations among which some diseases progress very rapidly and eventually lead to end stage chronic kidney failure, cirrhosis, chronic hepatitis, end stage heart failure, etc. In such cases, transplantation becomes the last life-saving alternative. However, when undergoing transplantation, patients require an effective and safe pharmacotherapy to avoid graft rejection or graft loss, prevent further complications and ensure a good quality of life. Hence, immunosuppressive therapies are critical and access to a quality medicine is essential to support the donation and transplantation process and to ensure patients can benefit from it.

3. Entity Supporting the Application and Requested Indications

3.1 Entity Supporting Application

The PAHO Blood Transfusion and Organ Transplants Advisor from the Medicines and Health Technologies Unit (HSS/MT) is requesting and supporting this application.

3.2 Requested Indications

Sirolimus, a target of rapamycin-inhibitor immunosuppressant, has been requested for the prophylaxis of organ rejection in adult patients receiving allogeneic renal transplants.

4. Medicine Characteristics and Pharmacological Information (*4-11*)

4.1 General Information

1) Medicine name (INN)	Sirolimus
2) ATC (anatomical therapeutic chemical- WHO Drug classification system)	L04AA06
3) Reference trade name: (1. Originator & 2. Non originator - when available some examples provided)	1. Originator: Rapamune (Pfizer) 2. Non originator: ■ Sirolimus 1mg; 2mg tab; (Dr Reddys Labs - FDA Tentative Approval) ■ Sirolimus 1mg; 2mg tab; (Vitae Lab) (COFREPRIS)
4) Therapeutic class (according to classification in the WHO EML)	Immunosuppressants – Target Of Rapamycin-Inhibitors (TOR-i). Not present in WHO EML.

4.2 Mechanism of Action

Sirolimus is an immunosuppressant that inhibits lymphocyte activation by binding to the specific cytosolic protein FK Biding Protein-12 (FKBP-12). The resulting immunosuppressive complex (FKBP-12-sirolimus) inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a regulatory protein involved in cell cycle progression. The inhibition of mTOR is responsible for blocking several specific signal transduction pathways from the G1 to the S phase of the cycle; thus leading to the inhibition of lymphocyte T activation and proliferation. Unlike cyclosporine and tacrolimus, sirolimus has no effect on calcineurin activity.

4.3 Pharmacokinetic/Pharmacodynamics Considerations

- *Absorption:*

  Following administration of sirolimus oral solution, the mean time to reach peak concentration was 1 hour in healthy patients and 2-3 hours in renal transplant patients. The bioavailability of sirolimus is low, 14% for the oral solution and 25% higher relative to the solution for the tablet. Sirolimus tablets are not considered bioequivalent to the solution although some clinical evidence has been demonstrated at the 2mg dose level.

- *Food effect:*

  Presence of food can alter the peak blood concentration (Cmax), the time to peak concentration (Tmax) and total exposure (AUC). However, the impact on the rate of absorption had no effect on the extent of absorption and on the efficacy of the drug. In order to minimize intervariability, sirolimus must be taken with or without food consistently. Grapefruit juice must be avoided during treatment with sirolimus considering the interaction with CYP3A4-mediated drug metabolism and Pgp mediated-drug transport.

- *Distribution:*

  Mean blood-to-plasma ratio 36 ± 17.9 (indicating sirolimus is partitioned in blood elements). Vd= 12 ± 7.52 L/kg. Plasma protein binding=92%.

- *Metabolism:*

  Sirolimus is a substrate of both cytochrome P450 3A4 and P-glycoprotein (P-gp). Extensive metabolism is done through O-demethylation and/or hydroxylation leading to 7 major metabolites in whole blood. Sirolimus is the major component in human blood and responsible for 90% of the immunosuppressive activity.

- *Excretion:*

  The mean elimination half-life of sirolimus (t½) after multiple dosing in stable renal transplant patients is approximately 62 ± 16 hours. 91% of the excretion is in feces and 2.2% in urine.

4.4 Use in Special Populations

- *Pregnant Women:*

  Category C: In certain animal studies sirolimus was embryo/fetotoxic. Although no current studies have been performed in pregnant women, sirolimus should be avoided during pregnancy. If used, the potential benefits should outweigh the potential risks to the embryo/fetus. For any women with child bearing potential, an effective method of contraception must be initiated before starting sirolimus, maintained during therapy and continued for 12 weeks after sirolimus is stopped.

- *Nursing Women:*

  It remains unknown if sirolimus is excreted in human milk. Sirolimus has been found in lactating rats. A decision should be made whether to avoid nursing or discontinue sirolimus, taking into account the importance of the medicine for the mother.

- *Pediatrics (<13 years of age):*

  The efficacy and safety in children less than 13 years have not been established. For children older than 13 years old considered at low-to-moderate immunological risk, the use of sirolimus (oral solution and tablets) is supported by evidence from well-controlled trials in pediatric renal transplantation patients. For pediatric patients considered at high-immunologic risk, the chronic use of sirolimus in combinations with calcineurin inhibitors and corticosteroids is not recommended based on a higher incidence of adverse events and no increased benefit.

- *Geriatric (> 65 years of age):*

  Performed clinical studies have not identified a difference in the elderly response compared to younger patients. However, the dose selection for this population should be done carefully considering the decrease in hepatic, renal and cardiac function or concomitant diseases and therapies.

- *Patients with hepatic impairment:*

  Because the clearance of sirolimus can be decreased in hepatic impaired patients, the maintenance dose of sirolimus should be reduced in this subpopulation. The blood through levels of sirolimus should be closely monitored and dose adjustments should be based upon monitoring results.

- *Patient with renal impairment:*

  No dose adjustment is required for this subpopulation.

4.5 Dosage, Preparation and Administration

- *Dosage and bioavailability generalities:*

  Sirolimus has to be administered once daily orally, consistently with or without food. It is not recommended to crush, chew or split tablets as the bioavailability has not been determined. If patients are unable to swallow entire tablet, they should be prescribed the sirolimus oral solution and be instructed on its use. The tablets and oral solution should be taken with water or orange juice. Grapefruit juice must be avoided.

  A dose of sirolimus tablets of 2mg is equal to 2mg of sirolimus oral solution. However, it remains unknown if higher doses are equivalent in terms of mg to mg therefore tablets and oral solution cannot be used interchangeably at doses higher than 2mg.

  Cyclosporine microemulsion increases absorption of sirolimus. If both medicines are part of the immunosuppressive therapy, sirolimus must be taken 4 hours after the administration of cyclosporine.

- *Dosage in patients at low-to-moderate-immunologic risk:*

  1. *Sirolimus and cyclosporine (combination therapy):* It is recommended that following transplantation, sirolimus should be initiated as soon as possible and administered concomitantly with cyclosporine and corticosteroids. Cyclosporine should be withdrawn 2 to 4 months after transplantation and sirolimus dose increased to reach the target blood concentration.

     The usual starting dose is 6mg and followed by 2mg once daily until monitoring results are available. Sirolimus dose should be adjusted and individualized with the aim of obtaining through levels of 4 to 12ng/ml (chromatographic assay).

2. *Sirolimus maintenance therapy (following cyclosporine withdrawal):* At 2 to 4 months after transplantation, cyclosporine should be gradually discontinued on a 4 to 8 week schedule and sirolimus through levels should reach 16 to 24ng/ml for the first year after transplant. After one year, the concentrations can be reduced to 12 to 20ng/ml.

- *Dosage in patients at high immunological risk:*

  Patients with a high immunological risk are defined as: black transplant recipients and/or repeat renal transplant, recipients who lost a previous allograft for immunologic reason and/or patients with high-panel reactive antibodies [PRA; peak PRA level > 80%].

1. *Sirolimus and cyclosporine (combination therapy):* For patient at high risk, the combination therapy should be administered for a period of one year. The efficacy and safety of the combination have not been studied further than one year and their further use should be considered based on the patient's clinical condition.
   The initial dose of sirolimus is 15mg the first day of transplantation followed by 5mg/day once daily aiming for through blood concentrations of 10-15 ng/ml. The starting dose of cyclosporine should be 7mg/kg/day (divided in 2 doses) with varying blood through concentration (see product monograph for more details). Prednisone should be administered at a minimum of 5mg/day.

- *Dosage adjustment and maximum dosage:*

  Considering the long half-life of sirolimus, caution is needed when adjusting the dose in the beginning of therapy as frequent changes might lead to overdosing or underdosing. When an equilibrium state is reached and a maintenance dose is defined, dose adjustments should be done at a 7-14 days interval based on concentration monitoring. The maximum dose of sirolimus is 40mg/day.

- *Administration:*

  Sirolimus tablets can be swallowed with water or orange juice. Sirolimus oral solution must be diluted prior to use. The prescribed amount of sirolimus must be drawn from the original bottle using an amber syringe, emptied in a plastic cup containing 60ml of water or orange juice, stirred vigorously and consumed at once. The container must be rinsed with an additional 120ml of water or orange juice and the mixture must be consumed at once to avoid any waste of medicine. *(Please see product monograph for detailed information on dilution and administration.)*

4.6 Contraindications

- Sirolimus is contraindicated in patient with hypersensitivity to sirolimus or to any of its derivatives or components. Sirolimus oral solution contains soya oil therefore patients allergic to soya or peanuts must avoid this medicine.

4.7 Warnings/Precautions

- *Lung transplantation:*

  Cases of bronchial anastomotic dehiscence, most fatal, have been reported when sirolimus has been used in de novo transplanted lung patients; therefore, its use is not recommended.

- *Liver transplantation: excess mortality, graft loss and hepatic artery thrombosis (HAT):*

  The efficacy and safety of sirolimus in liver transplanted patients has not been demonstrated therefore its use is not recommended. Studies conducted with sirolimus in combination with tacrolimus or cyclosporine have shown that there is an increase in adverse outcomes (mortality, graft loss, hepatic artery thrombosis) for this population.

- *Carcinogenesis and mutagenesis:*

  Sirolimus in combination with other immunosuppressive regimens have the increased risk of developing lymphomas and other malignancies, particularly of the skin. Limit exposure to sunlight and UV light, wear appropriate clothing and apply sunscreen with high protection factor to reduce the risk of skin malignancies.

- *Cardiovascular:*

  In patients treated with sirolimus, the triglycerides and serum cholesterol can be increased. The risk/benefit of sirolimus should be considered in patients with established hyperlipidemia. Any patient under sirolimus therapy should be monitored for hyperlipidemia and if detected, appropriate therapy should be initiated (diet, exercise, lipid-lowering agents). Concomitant administration with cyclosporine can further increase risk. If patients are administered HMG-CoA reductase inhibitors and/or fibrates, they should be monitored for possible development of rhabdomyolysis and other adverse events.

- *Endocrine and Metabolism:*

  Co-administration of sirolimus with strong inhibitors or inducer of the cytochrome 3A4 and/or P-glycoprotein (P-gp) can alter blood concentrations of the medicines (*See Drug Interactions*) therefore their use is not recommended.

- *Hematologic:*

  The use of sirolimus and other immunosuppressive therapies can increase the risk of developing leukopenia. Consider reducing the dose of the immunosuppressants if leukopenia develops.

- *Immunologic*

  An increase in immunosuppression can lead to opportunistic infections, sepsis and fatal infections. Activation of latent viral infections can arise such as BK virus associated nephropathy leading to renal deterioration and possibly renal graft loss or progressive multifocal leukoencephalopathy (PML), which can sometimes be fatal. Patient monitoring is crucial and reducing the immunosuppressive dosing should be considered if such outcomes arise. The risk that reduced immunosuppression represents for the graft has to be taken into account as well.

- *Musculoskeletal:*

  Sirolimus may impair or delay wound healing and/or fluid accumulation. Compared to other immunosuppressive agents, studies have showed that sirolimus had a higher rate of wound-healing complications such as lymphocele and was associated with a higher incidence of fluid accumulation such as peripheral edema, pleural effusion, pericardial effusion, etc.

- *Renal:*

  The use of sirolimus can impair renal function, increase mean serum creatinine and lower glomerular filtration rates. Combinations with other immunosuppressants that can impair renal function have to be carefully monitored. Appropriate adjustment in the dosing of immunosuppressive regimens and the selection of medicines used is important to diminish the risk to alter renal function of the graft. Urinary protein excretion can also be increased by sirolimus. Periodic monitoring is required.

- *Respiratory:*

  Some cases of interstitial lung disease, some fatal, have occurred in patients with sirolimus as part of the immunosuppressive therapy. Sirolimus discontinuation or dose reduction can sometimes resolve the adverse outcome. Caution is required.

- *Antimicrobial prophylaxis:*

  Cytomegalovirus (CMV) prophylaxis is required during 3 months post-transplantation to prevent infection. Antimicrobial prophylaxis for Pneumocystis carinii is required for a period of one year post transplantation to prevent pneumonia. Cases have been reported in patients not receiving prophylaxis for these potential infections.

4.8 Side Effects

The table below includes common adverse events reported from clinical trials and adverse events from post-marketing surveillance of sirolimus. Sirolimus was concomitantly administered with cyclosporine and corticosteroids during clinical trials; therefore, the adverse events presented must be considered accordingly. The adverse events from post marketing surveillance are reported voluntarily by a population using sirolimus; however, it is not always possible to determine their frequency or a causal relationship to the medicine.

Adverse Events from Clinical Trials (>30% occurrence)	Adverse Events from Post-Marketing Surveillance
■ *Body as a whole* Headache; lymphocoele; fever; peripheral oedema; pain ■ *Hematological/lymphatic* anemia; thrombocytopaenia ■ *Digestive system* Constipation; abdominal pain; nausea; diarrhea ■ *Metabolic/Nutritional* Hypertriglyceridaemia (hyperlipidaemia); hypokalemia; hyperglycemia; hypercholesterolemia; hypophosphatemia; increased creatinine increased lactate dehydrogenase (LDH); ■ *Cardiovascular* Hypertension ■ *Musculoskeletal, connective tissue and bone disorders* Arthralgia ■ *Renal and urogenital* Urinary tract infection ■ *Skin and subcutaneous tissue disorders* Acne	■ *Body as a Whole* Lymphedema ■ *Hematological/Lymphatic* pancytopenia, neutropenia ■ *Digestive System* Ascites ■ *Hepatobiliary Disorders* Hepatotoxicity, including fatal hepatic necrosis (with elevated sirolimus trough concentrations) ■ *Metabolic/Nutritional* Liver test abnormalities, AST and ALT increased, hypophosphatemia, hyperglycemia. ■ *Cardiovascular* Pericardial effusion; fluid accumulation ■ *Immune System* Hypersensitivity reactions, including anaphylactic/ anaphylactoid reactions, angioedema, and hypersensitivity vasculitis ■ *Infections* Tuberculosis. BK virus associated nephropathy (including deteriorating renal function and renal graft loss); progressive multifocal leukoencephalopathy (PML) sometimes fatal; *clostridium difficile;* enterocolitis. ■ *Respiratory* Interstitial lung disease (including pneumonitis, bronchiolitis obliterans organizing pneumonia [BOOP], and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred. Pulmonary hemorrhage; pleural effusion; alveolar proteinosis. ■ *Urogenital* Nephrotic syndrome, proteinuria, focal segmental glomerulosclerosis, ovarian cysts, amenorrhea, menorrhagia). Azoospermia (reversible upon discontinuation of sirolimus) ■ *Skin* – Exfoliative dermatitis

4.9 Main Interactions

Sirolimus is extensively metabolized by CYP3A4 isoenzymes and is transported from the intestines enterocytes by the P-glycoprotein (Pgp) drug-efflux pump. Any drug that can alter the functioning of these proteins can also affect the absorption and elimination of sirolimus and leading to drug-to-drug interactions. The following table provides examples of such interactions.

Drug	Interactions
Inhibitors of CYP3A4 and/or PgP: ■ Calcium channel blockers: diltiazem, verapamil ■ Antifungal agents: clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole ■ Antibiotics: clarithromycin, erythromycin ■ Gastrointestinal prokinetic agents: cisapride, metoclopramide ■ Other drugs: bromocriptine, cimetidine, cyclosporine, danazol, protease inhibitors (e.g. for HIV and hepatitis C that include drugs such as ritonavir, indinavir, boceprevir and telaprevir)	Inhibitors of CYP3A4 and Pgp can decrease metabolism and increase sirolimus concentrations in the blood. The administration of sirolimus concomitantly with strong inhibitors of CYP3A4 (ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) is not recommended. Monitoring of blood concentration levels and appropriate dosing adjustments should be done when other substrates or inhibitors of CYP3A4 are administered concomitantly with sirolimus.
Inducers of CYP3A4 and/or PgP: ■ Anticonvulsants: carbamazepine, phenobarbitone, phenytoin ■ Antibiotics: rifabutin, rifampicin ■ Herbal preparations: St. John's Wort (Hypericum perforatum, hypericin).	Inducers of CYP3A4 increase the metabolism of sirolimus and can decrease sirolimus blood concentrations. Sub-therapeutic doses can lead to a loss of the medicine's efficacy. The administration of sirolimus concomitantly with strong inducers of CYP3A4 (rifampin, rifabutin) is not recommended. Monitoring of blood concentration levels and appropriate dosing adjustments should be done when other inducers of CYP3A4 are administered concomitantly with sirolimus.
Oral contraceptives	No pharmacokinetic interaction was observed between sirolimus and 0.3 mg norgestrel/ 0.03 mg ethinyl oestradiol; however, results cannot exclude interaction on a long-term treatment with sirolimus. Caution needed.
Vaccination	The use of live vaccines should be avoided. Vaccines efficacy may be altered.

4.10 Other

- *Storage:*

  Store bottles of sirolimus oral solution in the refrigerator at 36°F to 46°F (2°C to 8°C); Store sirolimus oral solution that is in a syringe at room temperature up to 77°F (25°C) or in the refrigerator at 36°F to 46°F (2°C to 8°C) for up to 24 hours; oral solution can be stored at room temperature up to 77°F (25°C) for maximum 15 days; Use the opened bottle of sirolimus within 1 month; Any diluted oral solution should be used immediately; Tablets can be stored at 20-25°C (68-77°F); Protect from light.

- *Assay for sirolimus therapeutic drug monitoring:*

  Sirolimus whole blood concentrations are measured by various chromatographic and immunoassay methodologies.

5. Alternatives to Sirolimus Available in the Strategic Fund

The current version of the Strategic Fund medicine list includes azathioprine and cyclosporine as immunosuppressant alternatives. Azathioprine and cyclosporine are listed on WHO Essential Medicine List.

The following document provides the supporting evidence regarding the comparison of sirolimus to calcineurin inhibitors (cyclosporine & tacrolimus) and antiproliferative metabolites (azathioprine & mycophenolate mofetil) in the treatment of adult kidney and heart transplant. This document does not represent a therapeutic guideline for treatment of these conditions and it is not intended for such use.

6. Guidelines Including the Use of the Medicine in Relation with the Proposed Indications

Below are presented some of the available guidelines related to organ transplantation.

- The Transplantation Society: KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients - 2009 http://www.tts.org/index.php?option=com_content&view=article&id=642&Itemid=246
- National Institute for Clinical Excellence (NICE): Immunosuppressive Therapy for Renal Transplantation in Adults - 2004 http://www.nice.org.uk/nicemedia/live/11544/32940/32940.pdf
- The International Society of Heart and Lung Transplantation Guidelines for the Care of Heart Transplant Recipients - 2010 http://download.journals.elsevierhealth.com/pdfs/journals/1053-2498/PIIS105324981000358X.pdf

7. Intervention and Summary of Evidence

The clinical questions presented below are based on the PAHO technical unit (HSS/MT) request to incorporate sirolimus in the Strategic Fund medicine list and input received from three Member States. The evidence presented in this section was obtained in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb).

The intervention and evidence summary has been compiled in three tables (*7.1-7.3*), with the corresponding Grading of Recommendations Assessment, Development and Evaluation (GRADE), and when relevant, characteristics of the critically reviewed clinical trials.

The evidence presented for use in kidney transplants (*tables 7.1 & 7.2*) is supported by systematic reviews. Due to the absence of a systematic review for heart transplants (*table 7.3*); the evidence presented is supported by a critical review of 3 clinical trials.

The search strategy and references supporting the intervention and summary of evidence for all three tables are available in *Section 9* of this dossier.

7.1 Sirolimus Compared to Calcineurin Inhibitors for Kidney Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of sirolimus compared to calcineurin inhibitors (cyclosporine, tacrolimus) in the treatment of adult kidney transplant?

CONTEXT	Sirolimus versus calcineurin inhibitors
Over the last past decades, renal transplantation has been established as the treatment of choice for many patients with end-stage renal failure. The only other current alternative is dialysis. The transplant rate is around 30 patients/million population. The establishment of transplantation was made possible by the introduction of immunosuppressants. Immunosuppression has customarily constituted triple therapy with: i) a calcineurin inhibitor (cyclosporine or tacrolimus); ii) an antiproliferative agent (azathioprine); and iii) a corticosteroid. People who undergo renal transplantation are required to receive life-long (or at least, long-term) treatment with immunosuppressive drugs. When selecting these treatments, the risk of immunologically mediated graft failure for any donor–recipient pair needs to be balanced against the drug's side effects for the recipient. The ultimate aim of treatment is to prolong patient and graft survival. Over the past decade, the introduction of new immunosuppressive drugs with new mechanisms of action has substantially increased options for new strategies that produce adequate immunosuppression to prevent acute rejection while simultaneously reducing the side effects associated with calcineurin inhibitor therapies. Target of rapamycin inhibitors (TOR-I), such as sirolimus, are among the newest agents introduced and their clinical role has to be compared to the other existing immunosuppressive agents.	

INTERVENTION	Sirolimus versus calcineurin inhibitors
Sirolimus does not show differences in mortality, total graft loss, or acute rejection rate compared to calcineurin inhibitors. *High quality evidence.*	
Sirolimus does not show differences in the risk of malignancy, new-onset diabetes requiring insulin or hypercholesterolemia compared to calcineurin inhibitors. *High quality evidence.*	
Sirolimus decreases serum creatinine compared to calcineurin inhibitors. *High quality evidence.*	
Sirolimus increases the calculated glomerular filtration rate compared to calcineurin inhibitors. *High quality evidence.*	
Sirolimus increases the risk of lymphocoele, bone marrow suppression or requirement of drug treatment for lipid disturbance compared to calcineurin inhibitors. *High quality evidence.*	

Summary of evidence	
Benefits	A Cochrane systematic review (*1*) assessed the benefits and harms of immunosuppressive regimens containing target of rapamycin inhibitors (TOR-I) such as sirolimus and everolimus, given in combination with any other immunosuppressive agents, when compared to other regimens as initial therapy for kidney transplant recipients. The eligibility criteria were restricted to RCTs and quasi-RCTs where drug regimens containing TOR-I were compared to alternative drug regimens in the immediate post-transplant period were included, without age restriction, dosage or language of report. The review included 22 studies (3,603 participants) assessing sirolimus versus other immunosuppressive agents. Outcomes were measured up to two years. In the review, pooled analyses were presented both in separate comparisons between sirolimus and cyclosporine or tacrolimus, or jointly as calcineurin inhibitors drugs. As the results for each of the calcineurin inhibitors (cyclosporine or tacrolimus) are similar for the main outcome measures, pooled results of studies in which the comparison interventions were cyclosporine or tacrolimus are presented here. The Cochrane review did not show statistically significant differences between sirolimus and the calcineurin inhibitors (cyclosporine or tacrolimus) in any of the relevant outcomes assessed (6 RCT; 631 patients; tacrolimus 2 RCT 264 patients; cyclosporine 4 RCT and 367 patients). Sirolimus and the calcineurin inhibitors showed similar rates of mortality (RR 0.98; 95%CI 0.39 to 2.48), total graft loss (RR 1.03; 95%CI 0.50 to 2.14) or acute rejection rate (RR 1.03; 95%CI: 0.74 to 1.44).
Risks	The assessed Cochrane systematic review (*1*) showed no statistically significant differences between sirolimus and the calcineurin inhibitors (cyclosporine or tacrolimus) in relation with the risk of malignancy at two years (3 RCT, 447 patients; RR 0.66; 95%CI 0.10 to 4.46; tacrolimus 1 RCT 141 patients; cyclosporine 3 RCT and 306 patients), new-onset diabetes requiring insulin at one year (3 RCT 244 patients: RR 1.25; 95%CI 0.53 to 2.95; tacrolimus 1 RCT 83 patients; cyclosporine 2 RCT and 161 patients), hypercholesterolemia at one year (2 RCT 161 patients; RR 1.95; 95%CI 0.92 to 4.14). On the other hand sirolimus, compared with calcineurin inhibitors, showed a statistically significant decrease of serum creatinine (mg/dL) (4 RCT, 255 patients: MD -0.21; 95%CI: -0.35 to -0.06; tacrolimus 1 RCT, 99 patients; cyclosporine 3 RCT, 156 patients), and an increase in the calculated glomerular filtration rate (mL/min) (3 RCT, 186 patients; MD 14.94; 95%CI 9.33 to 20.55; tacrolimus 1 RCT, 99 patients; ciclosporin 2 RCT, 156 patients). Regarding other adverse events, compared with calcineurin inhibitors treated patients, sirolimus treated patients had increased risk of lymphocele (3 RCT; RR 3.06; 95%CI 1.59 to 5.91), and were more likely to have bone marrow suppression (anemia, (3 RCT): RR 1.67; 95%CI 1.27 to 2.20; leucopenia, (2 RCT): RR 2.02; 95%CI 1.12 to 3.66; thrombocytopenia (3 RCT): RR 6.97; 95% CI 2.97 to 16.36). They were also more likely to require drug treatment for lipid disturbance (4 RCT; RR 1.78; 95%CI 1.06 to 2.98), but less likely to experience tremor (3 RCT; RR 0.15; 95%CI 0.05 to 0.42).
Comments/ Applicability	Authors of the Cochrane systematic review (*1*) considered that the main limitation of the available evidence was that of the trials included in the review. Data in these trials was limited beyond two years post-transplantation. Additionally, where graft-focussed outcomes were well reported, many of the potentially informative patient-focussed adverse outcomes were not reported, not defined, or inconsistently reported. Transplant clinicians have become habituated to the use of surrogate outcomes as the primary outcomes in trial design, and which inform choice of agents for patient care. Consistent with most trials in kidney transplantation, the trials in this review also focused on surrogate outcomes. Long-term 'hard' clinical outcomes in randomised trials, although clearly preferable, are time-consuming, and cost-prohibitive to adequately power trials around. Although evidence of a difference in outcome for a surrogate marker of patient or graft survival might reach statistical significance in meta-analysis, it should be recognised that this does not necessarily equate to the same difference in the longer-term outcome the surrogate seeks to inform.

Summary of evidence	
Comments/ Applicability	Authors of the Cochrane systematic review (*1*) considered that in order to determine if there will be long-term benefits of sirolimus strategies there are two possibilities; modelling differences in surrogate markers, such as early GFR, to predict long-term results, or to continue the long-term follow-up of trials to five years and beyond. Both strategies are problematic, as the former relies on a fixed relationship between short and long-term outcomes irrespective of drug treatment or other events and the latter relies on low drop-out and contamination rates and a significant commitment of both time and finance to coordinate patients, data and methodologically rigorous intention-to-treat (rather than 'on treatment') analyses.
Cost studies	A CRD assessed economic evaluation (*2*) synthesized a study aimed to estimate the cost-effectiveness of four triple immunosuppression regimens that were available for renal transplant patients in a secondary care setting in Germany (*3*). The analytical approach was a state-transition Markov model was used to estimate the cost-effectiveness of the triple immunosuppression regimens, from the perspective of the German Statutory Health Insurance (SHI) and the time horizon was 10 years. The main measures of benefit were the cost per life-year gained and the cost per year with a functioning graft gained. Future effects were discounted at a rate of 5% per year. A probabilistic sensitivity analysis was performed to test whether the results were robust to variations in the parameter estimates, to reflect the uncertainty in them. The mean cost per patient over two years was EUR 26,732 for sirolimus, EUR 29,352 for cyclosporine, EUR 33,415 for everolimus, and EUR 49,978 for tacrolimus treatment regimens. Over 10 years, the mean cost was EUR 100,758 for sirolimus, EUR 108,300 for cyclosporine, EUR 120,316 for everolimus, and EUR 183,802 for tacrolimus. The life-years gained per patient over two years were 1.910 for sirolimus, 1.915 for cyclosporine, 1.893 for everolimus, and 1.908 for tacrolimus. Over 10 years, they were 6.792 for sirolimus, 6.752 for cyclosporine, 6.606 for everolimus, and 6.839 for tacrolimus. Over a period of two years, everolimus and tacrolimus were dominated by sirolimus, as they were more costly and less effective. The incremental cost per life-year gained for cyclosporine versus sirolimus was EUR 524,000. Over 10 years, cyclosporine and everolimus were dominated by sirolimus, and the incremental cost per life-year gained for tacrolimus versus sirolimus was EUR 1,766,894.

Table 1. GRADE Evaluation of Clinical Outcomes: Sirolimus Versus Calcineurin Inhibitors for Kidney Transplant Recipients (Assessment from Data in Reference *1*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
6 (631)	Mortality	Sirolimus Calcineurin inhibitors	4	0	0	0	0	High	
6 (631)	Total graft loss	Sirolimus Calcineurin inhibitors	4	0	0	0	0	High	
6 (631)	Acute rejection rate	Sirolimus Calcineurin inhibitors	4	0	0	0	0	High	
3 (447)	Malignancy risk	Sirolimus Calcineurin inhibitors	4	0	0	0	0	High	
3 (244)	New, sustained diabetes requiring insulin	Sirolimus Calcineurin inhibitors	4	0	0	0	0	High	
2 (161)	Hypercholesterolemia	Sirolimus Calcineurin inhibitors	4	0	0	0	0	High	
4 (255)	Serum creatinine	Sirolimus Calcineurin inhibitors	4	0	0	0	0	High	
3 (186)	Glomerular filtration rate	Sirolimus Calcineurin inhibitors	4	0	0	0	0	High	
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

7.2 Sirolimus Compared to Antiproliferative Metabolites for Kidney Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of sirolimus compared to antiproliferative metabolites (mycophenolate mofetil, azathioprine) in the treatment of adult kidney transplant?

CONTEXT	Sirolimus versus antiproliferative metabolites
Over the last past decades, renal transplantation has been established as the treatment of choice for many patients with end-stage renal failure. The only current other alternative is dialysis. The transplant rate is around 30 patients/million population. The establishment of transplantation was made possible by the introduction of immunosuppressants. Immunosuppression has customarily constituted triple therapy with: i) a calcineurin inhibitor (cyclosporine or tacrolimus); ii) an antiproliferative agent (azathioprine); and iii) a corticosteroid. People who undergo renal transplantation are required to receive life-long (or at least, long-term) treatment with immunosuppressive drugs. When selecting these treatments, the risk of immunologically mediated graft failure for any donor–recipient pair needs to be balanced against the drug's side effects for the recipient. The ultimate aim of treatment is to prolong patient and graft survival. Over the past decade, the introduction of new immunosuppressive drugs with novel mechanisms of action has substantially increased options for new strategies that produce adequate immunosuppression to prevent acute rejection while simultaneously reducing the side effects associated with calcineurin inhibitor therapies. Target of rapamycin inhibitors (TOR-I), such as sirolimus, are among the newest agents introduced and their clinical role has to be compared to the other immunosuppressive agents.	

INTERVENTION	Sirolimus versus antiproliferative metabolites
Sirolimus does not show differences in mortality, total graft loss, or acute rejection compared to antiproliferative metabolites. *High quality evidence.*	
Sirolimus does not show differences in the risk of malignancy or new-onset diabetes requiring insulin compared to antiproliferative metabolites. *High quality evidence.*	
Sirolimus increases the risk of hypercholesterolemia compared to antiproliferative metabolites. *High quality evidence.*	
Sirolimus increases serum creatinine compared to antiproliferative metabolites. *High quality evidence.*	

Summary of evidence	
Benefits	A Cochrane systematic review (*1*) assessed the benefits and harms of immunosuppressive regimens containing target of rapamycin inhibitors (TOR-I) such as sirolimus and everolimus, given in combination with any other immunosuppressive agents, when compared to other regimens as initial therapy for kidney transplant recipients. The eligibility criteria were restricted to RCTs and quasi-RCTs where drug regimens containing TOR-I were compared to alternative drug regimens in the immediate post-transplant period were included, without age restriction, dosage or language of report. The review included 22 studies (3,603 participants) assessing sirolimus versus other immunosuppressive agents. Outcomes were measured up to two years. As the pooled analyses in the review were presented combining data for studies in which the compared TOR-I could be sirolimus or everolimus, the results presented here are limited to those studies evaluating sirolimus.

continues

Summary of evidence	
Benefits *(cont.)*	The Cochrane review did not show statistically significant differences between sirolimus and azathioprine or mycophenolate in any of the relevant outcomes assessed (9 RCT; 2,743 patients; azathioprine 2 RCT, 789 patients; mycophenolate 7 RCT, 1954 patients). Sirolimus and antiproliferative metabolites showed similar rates of mortality (RR 1.10; 95%CI 0.67 to 1.81), total graft loss (RR 1.08; 95%CI 0.81 to 1.44) or acute rejection rate (RR 0.84; 95%CI: 0.65 to 1.10).
Risks	The assessed Cochrane systematic review (1) did not show differences between sirolimus and azathioprine or mycophenolate in relation with the risk of malignancy (5 RCT, 2,356 patients; RR 0.69; 95%CI 0.36 to 1.35; azathioprine 2 RCT, 779 patients; mycophenolate 3 RCT, 1577 patients) or new-onset diabetes requiring insulin (5 RCT, 2, 012 patients; RR 0.97; 95%CI 0.68 to 1.39; azathioprine 1 RCT, 710 patients; mycophenolate 4 RCT, 1302 patients). On the other hand sirolimus, compared with azathioprine or mycophenolate, showed a statistically significant increased risk of hypercholesterolemia (4 RCT, 1,899 patients; RR 1.73; 95%CI 1.14 to 2.63; azathioprine 2 RCT, 779 patients; mycophenolate 2 RCT, 1120 patients), and an increase of serum creatinine (µmol/L) (6 RCT, 1,142 patients: MD 21.46; 95%CI: 7.93 to 35.00; azathioprine 2 RCT, 492 patients; mycophenolate 4 RCT, 650 patients).
Comments/ Applicability	Authors of the Cochrane systematic review (*1*) considered that the main limitation of the available evidence was that of the trials included in the review. Data in these trials was limited beyond two years post-transplantation. Additionally, where graft-focussed outcomes were well reported, many of the potentially informative patient-focussed adverse outcomes were not reported, not defined, or inconsistently reported. Transplant clinicians have become habituated to the use of surrogate outcomes as the primary outcomes in trial design, and which inform choice of agents for patient care. Consistent with most trials in kidney transplantation, the trials in this review also focused on surrogate outcomes. Long-term 'hard' clinical outcomes in randomised trials, although clearly preferable, are time-consuming, and cost-prohibitive to adequately power trials around. Although evidence of a difference in outcome for a surrogate marker of patient or graft survival might reach statistical significance in meta-analysis, it should be recognised that this does not necessarily equate to the same difference in the longer-term outcome the surrogate seeks to inform.
	Authors of the Cochrane systematic review (*1*) considered that in order to determine if there will be long-term benefits of sirolimus strategies there are two possibilities; modelling differences in surrogate markers, such as early GFR, to predict long-term results, or to continue the long-term follow-up of trials to five years and beyond. Both strategies are problematic, as the former relies on a fixed relationship between short and long-term outcomes irrespective of drug treatment or other events and the latter relies on low drop-out and contamination rates and a significant commitment of both time and finance to coordinate patients, data and methodologically rigorous intention-to-treat (rather than 'on treatment') analyses.
Cost studies	The search did not retrieve relevant economic evaluations assessing the cost-effectiveness of sirolimus and antiproliferative metabolites in renal transplantation.

Table 1. GRADE Evaluation of Clinical Outcomes: Sirolimus Versus Antiproliferative Metabolites for Kidney Transplant Recipients (Assessment from Data in Reference *1*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
9 (2743)	Mortality	Sirolimus Antiproliferative metabolites	4	0	0	0	0	High	
9 (2743)	Total graft loss	Sirolimus Antiproliferative metabolites	4	0	0	0	0	High	
9 (2800)	Acute rejection rate	Sirolimus Antiproliferative metabolites	4	0	0	0	0	High	
5 (2356)	Malignancy risk	Sirolimus Antiproliferative metabolites	4	0	0	0	0	High	
5 (2012)	New, sustained diabetes requiring insulin	Sirolimus Antiproliferative metabolites	4	0	0	0	0	High	
4 (1899)	Hypercholesterolemia	Sirolimus Antiproliferative metabolites	4	0	0	0	0	High	
6 (1142)	Serum creatinine	Sirolimus Antiproliferative metabolites	4	0	0	0	0	High	
7 (1221)	Glomerular filtration rate	Sirolimus Antiproliferative metabolites	4	0	0	0	0	High	
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

7.3 Sirolimus Compared to Calcineurin Inhibitors and Antiproliferative Metabolites for Heart Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of sirolimus compared to calcineurin inhibitors (cyclosporine, tacrolimus) and antiproliferative metabolites (mycophenolate mofetil, azathioprine) in the treatment of heart transplant?

CONTEXT	Sirolimus versus calcineurin inhibitors or antiproliferative metabolites
Immunosuppressive agents are typically judged by their ability to reduce acute rejection without adding toxicity (*1*). Until the last decade, the standard immunosuppressive regimen for cardiac transplantation patients consisted of cyclosporine (CYA), azathioprine (AZA) and corticosteroids. Because of the significant adverse effects attributed to these anti-rejection medications, and in an effort to further reduce both acute and chronic rejection, newer immunosuppressive agents had been developed (*2*). The m-TOR inhibitor sirolimus has been shown to slow progression of cardiac allograft vasculopathy in heart recipients with established angiographic disease (*1*). Tacrolimus (TAC) is a calcineurin inhibitor like CYA. It has been associated with lower rates of rejection and fewer adverse effects in liver, kidney, and pancreas transplantation (*2*). Mycophenolate mofetil (MMF) suppresses purine synthesis, leading to reduced proliferation of T and B lymphocytes (*3*).	

INTERVENTION	Sirolimus versus calcineurin inhibitors or antiproliferative metabolites
Sirolimus 3 or 5mg reduces the episodes of acute rejection compared to azathioprine. *Very low quality evidence.*	
Sirolimus 5mg increases mean serum creatinine levels compared to azathioprine. *Very low quality evidence.*	
Sirolimus 3 or 5mg increases the risk of pneumonia compared to azathioprine. *Very low quality evidence.*	
Sirolimus 5mg reduces the risk of cytomegalovirus systemic infection compared to azathioprine. *Very low quality evidence.*	
Sirolimus 3 or 5mg does not show differences in the rate of sepsis, herpes simplex, herpes zoster or tissue-invasive cytomegalovirus compared to azathioprine. *Very low quality evidence.*	
The combination of tacrolimus and sirolimus, tacrolimus and mycophenolate mofetil or cyclosporine and mycophenolate mofetil does not show differences in the rate of ≥3A rejection, hemodynamic compromise rejection, or requirement of antihypertensive therapy. *Very low quality evidence.*	
The combination of tacrolimus and sirolimus increases the median serum creatinine compared to the combination of tacrolimus and mycophenolate mofetil or cyclosporine and mycophenolate mofetil. *Very low quality evidence.*	
The combination of sirolimus and mycophenolate mofetil, tacrolimus and sirolimus or tacrolimus and mycophenolate mofetil does not show differences in the rate of acute rejection. *Very low quality evidence.*	
The combination of sirolimus and mycophenolate mofetil, tacrolimus and mycophenolate mofetil or tacrolimus and sirolimus does not show differences in survival at 5 years. *Very low quality evidence.*	
The combination of sirolimus and mycophenolate mofetil, tacrolimus and mycophenolate mofetil or tacrolimus and sirolimus does not show differences in the period freedom from cardiac allograft vasculophaty. *Very low quality evidence.*	

Summary of evidence	
Benefits	The search did not retrieve systematic reviews assessing the effectiveness of sirolimus (SRL) compared to calcineurin inhibitors (Cyclosporine (CYA); Tacrolimus (TAC)) and antiproliferative metabolites (Mycophenolate mofetil (MMF); Azathioprine (AZA)) in treatment of heart transplant. A specific search for trials found 3 clinical trials. One compared directly SRL versus AZA, and the remaining compared different combinations for SRL (SRL and TAC or SRL and MMF). The first trial was a randomized open label study (*1*) that compared SRL with AZA in combination with CYA and steroids administered from the time of cardiac transplantation. Cardiac transplant centers in Australia and New Zealand enrolled 136 heart transplant recipients that were followed for 12 months with safety observations up to 24 months. The aim of the trial was to determine the effect of SRL, used from the time of transplantation, on acute cellular rejection and graft vasculopathy in human heart transplantation. The groups were well matched at baseline for all demographic parameters except weight, which was 10% higher in patients receiving SRL 3mg. The SRL loading dose was reduced to 10 mg and the maintenance dose to 3 mg/d, with new trough levels of 8 to 18ng/mL. CYA target trough levels were reduced by 25% to diminish the CYA/SRL pharmacokinetic interaction. The primary end point was the incidence of first occurrence of biopsy-confirmed acute rejection. The second trial (*2*) evaluated 343 adult men and women undergoing their first cardiac transplant. The patient baseline characteristics are outlined in the table 1. Patients were randomized within 24 h post-operatively in an open label 1:1:1 frequency to 1 of 3 immunosuppression regimens. The primary endpoint of this study was the incidence of international Society of Heart and Lung Transplantation (ISHLT) grade 3A or greater rejection or hemodynamic compromise rejection requiring therapy within the first 6 months. Finally a third trial (*3*) randomized 78 de novo cardiac transplant recipients to TAC/MMF (n=34), TAC/SRL (n=29), or SRL and MMF plus anti-thymocyte globulin (ATG) (n=15). Demographic and baseline characteristics of patients included in the intent-to-treat population analyses were similar in the 3 treatments groups (see table 2). Results from a study (*1*) showed that, compared with AZA, SRL 3 mg (1 RCT, 56.8% vs 32.4%, p=0.027) and SRL 5mg (1 RCT, 32.8% vs 56.8%, p=0.013) reduced the number of patients with acute rejection. The second trial (*2*) did not show statistically significant differences in its primary endpoint of 6-month incidence of ≥3A rejection or hemodynamic compromise rejection requiring treatment among groups compared (1 RCT, TAC/MMF 22,4%, TAC/SRL 24.3%, CYA/MMF 31.6%, p=0.271). On the other hand, results of secondary endpoints at 1 year did not show significant differences in rejection ≥3A or hemodynamic compromise rejection requiring treatment (p=0.056) among groups. However, TAC/MMF compared CYA/MMF reduced the rejection ≥3A or hemodynamic compromise rejection requiring treatment (23.4% vs 36.8%, p=0.029). The remaining trial (*3*) showed that, compared to TAC/MMF or TAC/SRL, SRL/MMF had a lower incidence of acute rejection episodes, but the difference was not significant (1 RCT; TAC/MMF 82.4%, TAC/SRL 85.2%, SRL/MMF 73.3%; TAC/MMF vs TAC/SRL p=0.45; TAC/MMF vs SRL/MMF p=0.73; TAC/SRL vs SRL/MMF p=0.34). Overall, 5-year survival after heart transplantation did not show statistical differences among the 3 treatment groups (1 RCT, TAC/MMF 85.3%, TAC/SRL 93.1%, SRL/MMF 86.7%; TAC/MMF vs TAC/SRL, p=0.31; TAC/MMF vs SRL/MMF, p=0.86; TAC/SRL vs SRL/MMF, p=0.47).

Summary of evidence	
Risks	Keogh evaluated the incidence of infections, mean serum creatinine levels and discontinuation from the study (*1*). Compared with AZA, patients assigned to SRL 3mg and SRL 5mg had higher incidence of pneumonia (1 RCT, 4/34 (11.8%) SRL 3mg, 6/58 (10.3%) SRL 5mg, 0/44 (0%) AZA). SRL showed a lower incidence of cytomegalovirus infections, but the difference only was significant in the comparison between SRL 5mg and AZA (1 RCT, 4/34 (11.7%) SRL 3mg, 1/58 (1.7%) SRL 5mg, 9/44 (20.4%) AZA). No differences were showed between SRL and AZA regarding sepsis, herpes simplex, herpes zoster, and tissue-invasive cytomegalovirus. At 12 months, the patients assigned to SRL 5 mg showed a mean serum creatinine levels significantly higher than azathioprine (1 RCT, 165.1 vs 125.4, p<0.001). No statistically significant differences were found between sirolimus and azathioprine regarding discontinuation from the study at 12 months (1 RCT, 44% SRL 3mg, 32% SRL 5 mg, 40% AZA). Kobashigawa (*2*) showed that the incidence of individual adverse events was comparable among the three treatment groups at 1 year. The trial showed statistically significant differences in median serum creatinine (1 RCT; CYA/MMF 1.5, TAC/SRL 1.5, TAC/MMF 1.3, p = 0.032). In those patients with a baseline serum creatinine level was >1.5 mg/dL, the highest median serum creatinine was observed in the TAC/SRL group (p = 0.045), while values were comparable between TAC/MMF and CYA/MMF groups. Median systolic blood pressure increased from baseline in all treatment groups, but there were no statistically significant differences among the groups with respect to the percentage of patients who required antihypertensive treatment during the study (1 RCT, TAC/MMF 79%, TAC/SRL 76%, CYA/MMF 82%, p=0.271). Kaczmarek (*3*) showed that compared to TAC/MMF and TAC/SRL, SRL/MMF had higher period freedom from cardiac allograft vasculophaty at 5 years, but without statistical differences amongst the three groups (1 RCT, TAC/MMF 73.5%, TAC/SRL 80.8%, SRL/MMF 93.3%; p=0.32 (TAC/MMF vs TAC/SRL); p=0.09 (TAC/MMF vs SRL/MMF); p=0.32 (TAC/SRL vs SRL/MMF). Compared with TAC/MMF group, SRL/MMF group preserved renal function (1 RCT, mean levels of serum creatinine were TAC/MMF 1.44+/-0.65, SRL/MMF 1.25+/-0.46).
Comments/ Applicability	The results from the assessed trials should be considered in the light of several issues related to their validity. The assessed interventions, measured outcomes and adverse events reported were defined and measured in different ways within the different studies, resulting in a source of inconsistency between the trial results.
	The results of assessed trials should be interpreted with caution in light of their risk of bias due to discrepancies between an intention to treat and a drug-combination-received analysis, small sample sizes, or the lack of detailed information about the characteristics of included patients.
	The trials were supported by Astellas, Roche, Wyeth, and Fujisawa Healthcare Inc.
Cost studies	The search did not retrieved relevant economic evaluations assessing the cost-effectiveness of sirolimus and antiproliferative metabolites or calcineurin inhibitors in heart transplantation.

Table 1. Demographic and Baseline Characteristics in Kobashigawa (2)¥

	TAC/SRLn=111	TAC/MMFn=108	CYA/MMFn=115
Age, mean, yr	54.3	54.5	51.9
Gender, % male	82	81	73
Race/ethnicity, %			
White	80	89	79
Black	14	8	17
Asian	2	1	1
Hispanic	4	2	2
Indication for cardiac transplant, %			
Idiopathic	39.6	34.3	36.5
Ischemic	50.5	54.6	49.6
Valvular	5.4	3.7	6.1
Congenital	1.8	2.8	0.9
Other	2.7	4.6	7.0
Cholesterol, mg/dL (n)	151 (100)	157 (94)	151 (101)
LDL, mg/dL (n)	88 (92)	93 (92)	85 (89)
HDL, mg/dL (n)	38 (96)	37 (87)	38 (91)
Systolic blood pressure, mm Hg (n)	110 (105)	112 (104)	112 (114)
Diastolic blood pressure, mm Hg (n)	66 (105)	64 (104)	66 (114)
Serum creatinine, mg/dL	1.30 (110)	1.10 (108)	1.10 (115)
Diabetes mellitus, %	21.6	28.7	27.8
Hypertension Ж	34.2	36.1	37.4
Hyperlipidemia Ф	53.2	60.2	50,4
Donor age, yr, mean	30.7	34.3	33.3

¥ Values are medians unless otherwise indicated
Ж Hypertension is defined as a systolic blood pressure ≥140mmHg or a diastolic blood pressure ≥90 mmHg or receiving treatment.
Ф Hyperlipidemia is defined as total
TAC/SRLn: tacrolimus plus sirolimus
TAC/MMFn: tacrolimus plus mycophenolate mofetil
CYA/MMFn: Cyclosporine plus mycophenolate mofetil

Table 2. Demographic and Baseline Characteristics in Kaczmarek (3)¥

	TAC/MMF	TAC/SRL	SRL/MMF
Mean recipient age (years)	49.6 +/- 13.2	48.3 +/- 12.3	55.1 +/- 8.6
Mean donor age (years9	37.7 +/- 15.1	36.1 +/- 13.4	38.6 +/- 14.3
Male/female	28/6	27/2	10/5
Ischemic times (minutes)	238 +/- 47	246 +/- 50	225 +/-50

TAC/MMFn: Cyclosporine plus mycophenolate mofetil
TAC/ SRLn: Tacrolimus plus sirolimus
SRL/MMFn: Sirolimus/Mycophenolate mofetil

Table 3. GRADE Evaluation of Clinical Outcomes: Sirolimus Versus Calcineurin Inhibitors or Antiproliferative Metabolites for Heart Transplant Recipients (Assessment from Data in Reference *1-3*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
1 (136) (1)	Episodes of acute rejection; Mean serum creatinine levels; Discontinuation; Pneumonia; Cytomegalovirus systemic infections	SRL 3mg SRL 5mg AZA	4	-2	0	0	-1	Very Low	QUALITY: The trial drug was not blinded to clinicians or patients but was blinded to pathologists and intracoronary ultrasound (ICUS) core laboratory personnel. Analysis on an intent-to-treat dose basis is somewhat arbitrary, because for the latter half of trial, doses were adjusted according to level of SRL. PRECISION: low sample size
1 (343) (2)	Incidence of ≥3A rejection or hemodynamic compromise rejection requiring treatment incidence of pneumonia; Cytomegalovirus systemic infections; Mean serum creatinine levels; Discontinuation	TAC/MMF TAC/SRL CYA/MMF	4	-2	0	0	-1	Very Low	QUALITY: There were discrepancies between intent-to-treat and a drug-combination received analysis. On the other hand, TAC blood levels were more higher in TAC/MMF combination than TAC/MMF and TAC/SRL PRECISION: low sample size and event rate.

Table 3. GRADE Evaluation of Clinical Outcomes: Sirolimus Versus Calcineurin Inhibitors or Antiproliferative Metabolites for Heart Transplant Recipients (Assessment from Data in Reference *1-3*) (continued)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
1 (78) (3)	Period of freedom from cardiac allograft vasculopathy; Median levels of serum creatinine; Discontinuation	TAC/SRLn TAC/MMFn CYA/MMFn	4	-1	0	-1	-1	Very low	QUALITY: Authors does not mention of the study was blind and what were reasons of death from 9 patients during study. DIRECT EVIDENCE: The SRL/MMF group had an unusually high percentage of women (33%), which might have contributed to a higher number of rejection episodes. There were changed in medicaments without adjusted in analysis (e.g. Prednisolone was administered orally, and the dose was reduced from 1 to 0.1mg/kg/day) over a period of 4 weeks. After 6 months, prednisolone was withdrawn. PRECISIÓN: Small study cohort. Some parameters, such as freedom from CAV and freedom from CMV infection, revealed trends but no statistical significance.
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

8. Special Considerations and Additional Comments (*12-20*)

8.1 Regulatory Status of the Product in National Regulatory Authorities (NRAs)

The following table reflects the regulatory status of the product (originator and non originator – if applicable) in the 7 PAHO Region Reference NRAs (Argentina, Brazil, Canada, Colombia, Cuba, Mexico and United States) and the European Medicine Agency.

NRA	Status							
	0.5 mg Tab		1 mg Tab		2 mg Tab		1 mg/ml Oral Sol	
	Originator	Non Originator	Originator	Non Originator	Originator	Non Originator	Originator	Non Originator
Argentina (ANMAT)	x	---	x	---	x	---	x	---
Brazil (ANVISA)	x	---	x	---	x	---	x	---
Canada (Health Canada)	---	---	x	---	---	---	x	---
Colombia (INVIMA)	x	---	x	---	---	---	---	---
Cuba (CECMED)	---	---	---	---	---	---	---	---
Mexico (COFEPRIS)	---	---	x	x	x	x	x	---
USA (FDA)	x	---	x	Tentative Approval	x	Tentative Approval	x	---
Europe (EMA)	x	---	x	---	x	---	x	---

8.2 PAHO Member State Prices

Through ECONMED (an electronic listserv for public officials from the health sector), PAHO requested the price paid for procurement of sirolimus from Member States who utilize this products in their National Public Health Programs. Unfortunately, no data has been provided to PAHO by countries in Latin America and the Caribbean. PAHO will increase efforts to obtain some prices from Member States and will distribute the information when the committee convenes in Washington, D.C.

8.3 Results of PAHO Expression of Interest

For a medicine to be eligible for inclusion in the PAHO Strategic Fund medicine list, it must have supporting evidence of safety, efficacy, and clinical effectiveness. Additionally the product must satisfy one of the following criteria as related to the pharmaceutical market:

1. The acquisition of the medicines is subject to particular challenges related to product procurement, pricing, patent status, forecasting of future needs, and exclusivity contracts between pharmaceutical companies that restrict marketing in specific geographical areas.

2. Leveraging economies of scale (increases in the volume of medicine procured) can result in lower costs.

PAHO has established this criteria to ensure the inclusion of the product in the Strategic Fund will provide value added to Member States who procure this product through PAHO.

To evaluate these pharmaceutical market factors, the Procurement (PRO) Unit of PAHO conducted an Expression of Interest (EoI) to gather information related to the product. PRO contacted 19 suppliers, which are included in the PAHO approved supplier list, and asked for product data (i.e. available presentations, manufacturing origin & capacity, potential restrictions, prices, and available technical documents).

Limited response was obtained from the contacted suppliers; however, PRO believes sirolimus, does meet the pharmaceutical market criteria, specifically as there are limited sources that manufacture sirolimus. Currently, more manufacturers are beginning to produce the product (i.e. Dr. Reddy's Lab & Vitae Lab), which will improve competition. To overcome the potential challenges faced in procuring this product, the following are key recommendations made by PRO:

- Consolidate regional demand to leverage the benefits of economies of scale. If PAHO is able to obtain sufficient demand perform an international tender and establish Long Term Agreements with suppliers.
- Increase number of PAHO approved suppliers offering this product in order to ensure availability and create a more competitive market.

8.4 Potential Value Added for Procurement of the Medicine through the Strategic Fund

The current version of the Strategic Fund medicine list, published in April of 2013, may limit options in treatment of patients receiving transplants, as the Fund offers two immunosuppressive medicines (azathioprine & cyclosporine). If the presented evidence demonstrates adequate safety, efficacy, and clinical effectiveness, PAHO believes the inclusion of this product will improve Member States access to an effective and safe medicine that can be used to improve graft and patient survival in post-transplant therapy.

Reference pricing for sirolimus was not readily available; however, anecdotal data does indicate sirolimus is expensive in comparison to other immunosuppressive medicines. If included in the Strategic Fund List, PAHO would aim to consolidate regional demand to lower the costs of the product, thus easing the financial burden on Member States.

9. Search Strategy and References Supporting Intervention and Summary of Evidence

The interventions and summary of evidences presented in the three separate tables above in *Section VII.a-c* where all conducted with the same search strategy; however, each table yielded different results (selection criteria and the search strategy results). These differences are identified below is the table titled *Differences in the Selection Criteria and Search Results for each Clinical Question*. Additionally, the corresponding references for each clinical question are presented.

9.1 Inclusion Criteria

The aim of this evidence summary is to gather information from a systematic review about the benefits and risk of a drug in a specific health problem. For this reason we include in the summary the results from a rigorous systematic review, prioritizing Cochrane reviews. When a Cochrane review is not available or

it is not suitable to respond the scope of the clinical question, we consider the inclusion of a systematic review that at least: i) includes a clearly defined inclusion criteria; ii) reports a recent search in at least two databases; and iii) reports any efforts from authors to assess the risk of bias from the included studies.

These criteria are the minimum requirements established by the Centre for Reviews and Dissemination to include a systematic review in the Database of Abstracts of Reviews of Effects (DARE; www.crd.york.ac.uk/crdweb/AboutPage.asp). For the specific purposes of the "Cost studies" section we include the results from an economic evaluation, that is; a comparison of two or more interventions or care alternatives (including cost-benefit analyses, cost-utility analyses, and cost-effectiveness analyses).

9.2 Search for Studies

The inclusion criteria described above determines the search for the studies planned. We design specific search algorithms to search the AHRQ Effective Health Care Program and The Cochrane Library as the main source to retrieve high quality systematic reviews. Each search in these two resources is complemented with a search in MEDLINE (accessed through PubMed) with the purpose of check any additional or more recent systematic review. The search is performed without any limitation, with the exception of PubMed in which we limit the search to the validated subset of systematic reviews (systematic[sb]). As we included only economic evaluations in the "Cost studies" section we limit the search to the NHS EED Database. In those cases that the NHS EED Database does not provide relevant results, we perform a specific search in MEDLINE, limiting the search algorithm designed to retrieve systematic review with the term cost*[tiab]. The search to develop the present clinical question was performed in May 2013, with the search strategies detailed below (Section 9.4).

9.3 Rating the Quality of the Evidence

Each evidence summary provides a rating of the quality of evidence following the GRADE guidance. GRADE specifies four categories (high, moderate, low, and very low) that are applied to the body of evidence that supports each assessed outcome. In the context of a synthesis of the evidence the quality of evidence reflects the confidence that the estimates of the effect are correct. For each clinical question one experienced researcher collects in a table the number of studies and patients included in these studies that set the body of evidence for each specific outcome discussed in the "Benefits" and "Risks" sections. The quality of evidence is then rated for each specific outcome and a final category is provided, commenting the main limitations that compromise the quality of evidence. All the information collected in the table, and the details required to the rating of the quality of evidence are obtained from the assessed systematic review used to develop the evidence summary.

9.4 Selection Criteria

One experienced researcher screens the results from the search applying the inclusion criteria commented above. If a Cochrane review is identified, it is selected to develop the evidence summary. When a Cochrane review is not suitable to respond to the scope of the formulated clinical question, the references from MEDLINE are screened.

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
What is the efficacy and safety of sirolimus compared to calcineurin inhibitors (cyclosporine, tacrolimus) in the treatment of adult kidney transplant? What is the efficacy and safety of sirolimus compared to antiproliferative metabolites (mycophenolate mofetil, azathioprine) in the treatment of adult kidney transplant?	For the purposes of this clinical question, a Cochrane review was identified from the records retrieved from the Cochrane Database of Systematic Reviews (*1*).	**Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ transplantation 24 hits immunosuppress* 8 hits **Cochrane Database of Systematic Reviews: (The Cochrane Library; Issue 4 of 12, April 2013)** (transplantat* AND sirolimus):ti,ab,kw 667 hits (transplantat* AND target of rapamycin inhibitor*):ti,ab,kw 24 hits **MEDLINE (accessed via PubMed)** (transplant*[ti] AND (target of rapamycin inhibitor*[ti] OR sirolimus[ti])) AND systematic[sb] 20 hits
What is the the efficacy and safety of sirolimus compared to calcineurine inhibitors (cyclosporine, tacrolimus) and antiproliferative metabolites (mycophenolate mofetil, azathioprine) in the treatment of heart transplant?	For the purposes of this clinical question, no systematic reviews were available. A search in the Cochrane Central Register of Controlled Trials retrieved 44 references for clinical trials. The revision of their title and abstracts led to the exclusion of 36 references. We reviewed in detail 8 publications that resulted in the exclusion of 3 communications in Scientific Meetings and 2 prospective observational studies.	**Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ transplantation 24 hits immunosuppress* 8 hits **Cochrane Database of Systematic Reviews: (The Cochrane Library; Issue 4 of 12, April 2013)** (transplantat* AND sirolimus):ti,ab,kw 667 hits (transplantat* AND target of rapamycin inhibitor*):ti,ab,kw 24 hits **Cochrane Central Register of Controlled Trials : Issue 4 of 12, April 2013** (transplant*:ti AND (rapamycin OR sirolimus) AND (heart OR cardiac):ti) 40 hits **MEDLINE (accessed via PubMed)** (transplant*[ti] AND (target of rapamycin inhibitor*[ti] OR sirolimus[ti])) AND systematic[sb] 20 hits

9.5 References for the Clinical Question: What is the Efficacy and Safety of Sirolimus Compared to Calcineurin Inhibitors (Cyclosporine, Tacrolimus) in the Treatment of Adult Kidney Transplant?

1. Webster AC, Lee VWS, Chapman JR, Craig JC. Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. Cochrane Database of Systematic Reviews 2006, Issue 2. Art.No.: CD004290. DOI:10.1002/14651858.CD004290.pub2.
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2. References for the Clinical Question: What is the efficacy and safety of sirolimus compared to to calcineurine inhibitors (cyclosporine, tacrolimus) and antiproliferative metabolites (mycophenolate mofetil, azathioprine) in the treatment of heart transplant?
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10. Additional References

The following references are those cited in Section 2 (Public Health Relevance), Section 4 (Medicine Characteristics and Pharmacological Information) and Section 8 (Special Considerations and Additional Comments). References supporting the intervention and summary of evidence are available in Sections 9.5 - 9.6.

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2. Global observatory on Donation and Transplantation. [Internet]. 2013 [cited 2013 June 07]. Available at: http://www.transplant-observatory.org/Pages/Organs-Activity-Data.aspx.
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Annex 7

Review of the Available Evidence of Tacrolimus Capsule (0.5, 1 & 5mg) for Potential Inclusion in the Pan American Health Organization Strategic Fund Medicine List

Annex 7: Table of Contents

1. Introduction to the PAHO Strategic Fund

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (Strategic Fund) was created by the Director of the Pan American Health Organization (PAHO) at the request of Member States of the Organization, in September 1998 during the 35th session of the Pan American Sanitary Conference.

The Strategic Fund is a regional mechanism which aims to strengthen the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe and effective supplies at affordable prices obtained by leveraging the advantages of economies of scale.

To accomplish this objective the Strategic Fund publishes a list of medicines available for procurement in name of the Organization's Member States. The list utilizes as a foundation the World Health Organization (WHO) Essential Medicines List (EML); however, recently there has been a significant increase in Member State requests to procure products not included in the WHO EML.

In order to meet the needs of PAHO Member States the PAHO Director has created an external Expert Committee to review requests for inclusion of medicines not included in the WHO EML. This Expert Committee will allow PAHO to implement a decision making mechanism in agreement with concepts of quality, efficacy, safety and when available, information related to the value they provide in relation to their cost.

The committee will work exclusively on requests to update the SF medicine list, which will enable PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this EC should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

2. Public Health Relevance (*1-3*)

2.1 Organ Transplantation Situation Worldwide

Based on the WHO definition, transplantation refers to the transfer of human cells, tissues or organs from a donor to a recipient with the aim of restoring function in the body. Organ transplantation often times represents the last recourse treatment for patients with end stage diseases and organ failures. Transplantation is often the best alternative in terms of quality of life for the patient and cost effectiveness.

The WHO Global Observatory on Donation and Transplantation (GODT), a global database collecting transplantation data from Member States, states the 2008 analyzed data from 104 countries worldwide shows around 100,800 solid organ transplant are performed every year worldwide among which 69,400 are kidney transplants (46% from living donors), 20,200 liver transplants (14.6% from living donors), 5,400 heart transplants, 3,400 lung transplants and 2,400 pancreas transplants. Europe and the region of the Americas account for the majority of the countries with donation and transplantation programs.

Along with donation programs, transplantations have to be supported by a complex pharmacotherapy in order to prevent graft rejection and ensure the patient's survival. Access to an effective and safe immunosuppressive therapy is crucial in order to reach these important outcomes. However, in low-and-middle income countries access to effective medicine can sometimes constitute a real challenge and can compromise the overall survival of the transplanted population.

2.2 Organ Transplantation in the Americas

In 2011, the Global Observatory on Donation and Transplantation (GODT) stated 10,922 kidney transplants, 2,377 liver transplants, 425 heart transplants, 271 pancreas transplants, 110 lung transplants, and 9 small bowel transplants were performed in 18 countries from Latin America, which account for approximately 566.3 million habitants. Although not all countries from the Region have set up a national registry for organ transplantation, the trend illustrates the Region of the Americas, including the United States, is a leader in solid organ transplantation with the highest rates of heart, liver and kidney transplants in the world.

Low and middle-income countries includes the majority of the vulnerable populations among which some diseases progress very rapidly and eventually lead to end stage chronic kidney failure, cirrhosis, chronic hepatitis, end stage heart failure, etc. In such cases, transplantation becomes the last life-saving alternative. However, when undergoing transplantation, patients require an effective and safe pharmacotherapy to avoid graft rejection or graft loss, prevent further complications and ensure a good quality of life. Hence, immunosuppressive therapies are critical and access to a quality medicine is essential to support the donation and transplantation process and to ensure patients can benefit from it.

3. Entity Supporting the Application and Requested Indications

3.1 Entity Supporting Application

The PAHO Blood Transfusion and Organ Transplants Advisor from the Medicines and Health Technologies Unit (HSS/MT) is requesting and supporting this application.

3.2 Requested Indications

Tacrolimus, a calcineurin inhibitor, has been requested for the prophylaxis of organ rejection in adult patients receiving allogeneic renal, cardiac, bone marrow and stem cell or hepatic transplants.

4. Medicine Characteristics and Pharmacological Information (*4-10*)

4.1 General Information

1) Medicine name (INN)	Tacrolimus
2) ATC (anatomical therapeutic chemical- WHO Drug classification system)	L04AD02
3) Reference trade name: (1. Originator & 2. Non Originator - when available some examples provided)	1. Originator: Prograf 0.5, 1 & 5 mg (Astellas) 2. Non Originator: Tacrolimus 0.5, 1 & 5 mg (Accord, Mylan, Sandoz)
4) Therapeutic class (according to classification in the WHO EML)	This medicine is not present in WHO EML. The pharmacological class is immunosuppressant - calcineurin inhibitor

4.2 Mechanism of Action

The exact mechanism of action through which tacrolimus inhibits T-lymphocyte activation is not yet completely elucidated. Tacrolimus acts as an immunosuppressant by inhibiting the formation of cytotoxic lymphocytes, responsible for graft rejection. It acts as a suppressor of T-cell activation and T-helper-cell dependent B-cell proliferation and inhibits the formation of lymphokines (inerleukin-2,-3 gamma-interferon) and the expression of the interleukin-2 receptor. On a molecular level, tacrolimus binds to a cytosolic protein (FKBP-12). This protein is responsible for the accumulation of the compound. A complex of tacrolimus-FKBP-12 formed, calmodulin, calcium and calcineurin is formed and further inhibits the phosphatase activity of calcineurin.

4.3 Pharmacokinetic/Pharmacodynamics Considerations

- *Absorption:*

  Following oral administration of tacrolimus, the absorption to the systemic circulation from the gastrointestinal tract is incomplete. Considering the important inter-variability among patients, the therapy must be individualized for each patient. Dosing individualization can be achieved by monitoring therapeutic blood concentrations. The mean bioavailability varies between 17% and 23% among liver, heart, kidney transplant patients and healthy volunteers.

- *Food effect:*

  The presence and composition of food decreases the rate and extend of tacrolimus absorption. The oral bioavailability of tacrolimus decreases when the medicine is administered with or after a high fat meal. To maximize its bioavailability, tacrolimus must be taken separated from meals.

- *Distribution:*

  The volume of distribution of tacrolimus varies from 0.85 to 2.37 L/kg. Tacrolimus is highly bound to plasma proteins (99%) mainly albumin and alpha-1-acid-glycoprotein.

- *Metabolism:*

  Tacrolimus undergoes extensive hepatic metabolism, primarily by CYP3A4. Demethylation and hydroxylation are the main biotransformation mechanisms. Around 8 metabolites are produced among which 13-demethyl tacrolimus, known to have, in vitro, the same immunosuppressive activity as tacrolimus.

- *Excretion:*

  Less than 1% of the drug unchanged is excreted in the urine and feces. This indicates tacrolimus is almost completely metabolized before excretion. The elimination half-life is long, around 43 hours, and variable among populations. The main route of elimination is through fecal elimination (93%).

4.4 Use in Special Populations

- *Pregnant Women:*

  Category C. Tacrolimus crosses the placenta. In humans, the use of tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Animal studies have showed tacrolimus can lead to fetal malformations (cardiovascular, skeletal, omphalocele, gallbladder agenesis, ventricular hypoplasia, bulbous aortic arch, and others) and fetal death. Kidney hydronephrosis was also observed.

- *Nursing Women:*

  Tacrolimus is excreted in human milk. A decision whether to discontinue tacrolimus or discontinue breast-feeding must be considered, taking into consideration the importance of the drug to the mother.

- *Pediatrics:*

  Efficacy and safety in children receiving allogeneic kidney or heart transplants have not been established. Liver transplants have been performed successfully in pediatric patients up to 16 years old. Higher doses of tacrolimus were usually required to maintain similar blood through concentration to adult population.

- *Geriatric:*

  Although clinical trials have not identified differences in the elderly response compared to the younger population, dose selection in this population has to take into account the possible decrease in renal, cardiac and hepatic function as well as concomitant diseases and drugs. Start therapy at the lowest therapeutic dosage.

- *Renal impairment:*

  Consider the lower end therapeutic dosage in patients with liver or heart transplant that have pre-existent renal impairment.

- *Hepatic impairment:*

  Patients with severe hepatic impairment can have a lower clearance of tacrolimus compared to healthy patients. Liver transplant recipients experiencing hepatic impairment post-transplant can be associated with an increased risk of developing renal insufficiency. Some evidence suggests lower doses for these patients.

4.5 Dosage, Preparation and Administration

- *Dosing considerations:*

  Considering the inter-individual variability, dosing must be individualized. Factors that can alter dosing are: renal or hepatic impairment, race, pediatric use and concomitant use of other medicines. Tacrolimus IV should only be reserved to patients unable to take oral medication, in order to avoid risk of anaphylaxis. Substitution or change from immediate release tacrolimus to extended-release tacrolimus capsules should only be done under the close supervision of a transplant physician. Otherwise, patients should always be maintained on the same formulation to avoid change in blood concentration and potential graft loss. Maintain systemic exposure by ensuring adequate therapeutic drug monitoring and dose adjustments throughout therapy.

- *Dose in renal transplantation:*

  The recommended oral dose in renal transplant patients is 0.2-0.3mg/kg/day every 12 hours in two divided doses. The initial dose is administered within 24 hours of transplantation.

- *Dose in cardiac transplantation:*

  The recommended starting oral dose in cardiac transplant patients is 0.075mg/kg/day every 12 hours in two divided doses.

- *Dose in hepatic transplantation:*

  The recommended starting oral dose in cardiac transplant patients is 0.1-0.15mg/kg/day every 12 hours in two divided doses.

- *Conversion from IV therapy:*

  For cardiac and hepatic transplantation, the initial IV or oral dose should not be administered sooner than 6 hours post-transplant. If IV infusion is necessary when initiating therapy, switch to oral dose after 2-3 days if possible. The oral dose should be given 8-12 hours after last IV dose. Maintain low therapeutic dosing and monitor rejection symptoms and tolerability. Concomitant therapy with corticosteroid is suggested early post-transplant.

- *Administration:*

  Tacrolimus capsules (immediate release) have to be administered whole and not be crushed, cut or chewed. The capsules can be administered with or without food but should be administered consistently every day. Doses should be evenly distributed throughout the day.

4.6 Contraindications

- Tacrolimus is contraindicated if hypersensitivity to tacrolimus or any component or ingredient of the drug product.
- Tacrolimus (for IV injection) is contraindicated in patients with a hypersensitivity to HCO-60 (polyoxyl 60 hydrogenated castor oil).

4.7 Warnings/Precautions

- *Carcinogenesis and Mutagenesis (Lymphoma and Malignancy):*

  Similar to other immunosuppressive therapies, there is an increased risk of lymphomas and other malignancies, particularly of the skin, with the use of tacrolimus as an immunosuppressant compared to healthy patients. Appropriate measures to reduce the risk of skin cancer such as reducing exposure to sunlight and UV light, wearing protective clothing and use of sunscreen with high protection should be taken. Moreover, lymphoproliferative disorders associated with Epstein-Barr virus infection have been reported.

- *Cardiovascular:*

  Mild or moderate hypertension is a common side effect of tacrolimus that usually requires antihypertensive therapy. While most of the common antihypertensive medicines are used to treat it, potassium-sparing diuretics should be avoided as they increase the risk of hyperkalemia in combination with tacrolimus and calcium-channel blockers should be carefully administered as they might requires dose adjustments in the transplant patient. Heart failure, myocardial hypertrophy and arrhythmias have also been reported.

- *Hepatic/biliary:*

  Liver transplant patients experiencing post-transplant hepatic impairment have an increased risk of developing renal insufficiency related to high whole blood levels of tacrolimus. Use of lower doses and close monitoring is required in this population.

- *Hematologic:*

  Cases of pure red cell aplasia (PRCA) have been reported with the use of tacrolimus. Discontinue tacrolimus if other causes have been ruled out.

- *Immune/infections:*

  There is an increased risk of infection, particularly opportunistic infections, and activation of latent viral infections such as BK virus associated nephropathy and JC virus associated progressive

multifocal leukoencephalopathy (PML). High immunosuppressive therapies increase the risk of these infections that can lead to serious and fatal conditions. Physician should consider these risks when deteriorating renal function or neurological symptoms appear in patients. Close monitoring is required.

- *Neurologic:*

  The use of high doses of tacrolimus can lead to neurotoxicity including tremor, headache, changes in motor function and status, seizure, coma and delirium. The majority of these events have been associated with high whole blood or plasma concentrations of tacrolimus and some can respond to dosage adjustments. Posterior reversible encephalopathy syndrome (PRES) including headache, seizures and altered mental status have been reported. Patients usually respond positively after immediate discontinuation of tacrolimus upon diagnosis.

- *Renal:*

  Nephrotoxicity, characterized by an increase in serum creatinine, has been observed in renal, hepatic and cardiac transplant patients treated with tacrolimus. Impaired renal function requires close monitoring and tacrolimus dosage reduction. If dosing reduction does not improve renal function, change of immunosuppressive therapy should be considered. Mild to severe hypokalemia has also been reported. Serum potassium levels should be closely monitored and potassium-sparing diuretics should not be used in combination with tacrolimus therapy.

- *Pancreatic:*

  Increased whole blood through concentrations of tacrolimus, in combination with high doses of other immunosuppressants such as corticosteroids, can increase the risk of post-transplant diabetes mellitus (PTDM). Insulin dependent diabetes is associated with the use of tacrolimus, which can sometimes be reversed with a decrease in tacrolimus dose but can also become irreversible after prolonged tacrolimus administration. Close monitoring is required and the need for insulin therapy assessed periodically.

4.8 Side Effects

The following table includes adverse events reported from clinical trials and adverse events from post-marketing surveillance of tacrolimus. Adverse events retrieved from clinical trials may not necessarily reflect the ones observed in practice because of underlying conditions or concomitant use of other medicines. However, post marketing adverse reactions are reported voluntarily from the population. The frequency and the causal relationship to the drug cannot always be accurately estimated. For each type of adverse event in this section, some examples are provided. Please refer to the product monograph for additional information.

Common Adverse Events from Clinical Trials (kidney, heart and liver transplant)	Adverse Events from Post-Marketing Surveillance
■ Tremor ■ Headache ■ Diarrhea ■ Abdominal pain ■ Nausea ■ Pain ■ Fever ■ Asthenia ■ Hypomagnesemia ■ Hyperkalemia ■ Hyperglycemia ■ Hypertension ■ Hyperlipidemia ■ Urinary tract infection ■ Others	■ Cardiovascular: atrial fibrillation, cardiac arrhythmia, QT prolongation, ventricular fibrillation ■ Gastro intestinal: colitis, gastroenteritis, hepatotoxicity ■ Hemic/lymphatic: agranulocytosis, hemolytic anemia, neutropenia ■ Infections: progressive multifocal leukoencephalopathy (sometimes fatal), polyoma-virus associated nephropathy ■ Metabolic: glycosuria, weight decrease ■ Nervous system: hemiparesis, mental disorder ■ Respiratory: acute respiratory distress syndrome, interstitial lung disease ■ Skin: steven-johnson syndrome, toxic epidermal necrolysis ■ Urogenital: acute renal failure, hemolytic-uremic syndrome ■ Special senses: photophobia

4.9 Main Interactions

The table below provides some examples of medicines that can interact with tacrolimus; however, this is not an exhaustive list of interactions. Please refer to the product monograph for additional information.

Drug	Interaction
Drugs interactions that can affect renal function including but not limited to: ■ Aminoglycosides ■ Amphotericin B ■ Ganciclovir ■ Acyclovir ■ Cisplatin ■ NSAIDs ■ Cyclosporine	These medicines can additionally increase or aggravate renal impairment when administrated concomitantly with tacrolimus. NSAIDs can aggravate blood pressure and increase serum creatinine. Co-administration with cyclosporine can further increase nephrotoxicity therefore 24 hours must separate the last cyclosporine dose from tacrolimus and vice versa.
Drug interactions affecting blood concentrations of tacrolimus: ■ CYP3A and P-glycoprotein inhibitors and /or substrates: ■ Azole antifungals (ketoconazole, itraconazole, fluconazole) ■ Calcium channel blockers(diltiazem, verapamil) ■ GI prokinetic agents (cisapride, metoclopramide) ■ Antibiotics (clarithromycin, erythromycin) ■ Protease inhibitors (ritonavir, nelfinavir) ■ Other (cimetidine, cyclosporine)	Co administration of tacrolimus and CYP3A and/ or P-glycoprotein inhibitors will result in decreased tacrolimus metabolism and increased bioavailability resulting in an increase of blood concentration levels. For some of the mentioned medicines, a dosage adjustment of tacrolimus is necessary.
Drug interactions affecting blood concentrations of tacrolimus: ■ CYP3A inducers: ■ Anticonvulsants: (carbamazepine, phenytoin) ■ Anti-infectives: (rifampicin, rifabutin) ■ Herbal preparation: St- John's Wort	Co administration of tacrolimus and CYP3A and/or P-glycoprotein inducers will result in increased tacrolimus metabolism and decreased bioavailability resulting in a decrease of blood concentration levels. Sub-therapeutic doses can increase the risk of graft rejection. For some of the mentioned medicines, a dosage adjustment of tacrolimus is necessary to avoid important decrease in blood concentration. In most cases, a dosage adjustment of tacrolimus is necessary.

Drug	Interaction
Vaccines	The use of live vaccines should be avoided during treatment with tacrolimus. Also, other vaccinations may be less effective due to immunosuppression.
Food (grapefruit juice)	Grapefruit juice affects the P450 3A-mediated metabolism and should be avoided.

4.10 Other

- *Storage:*

  Store between 5°C and 25°C (41°F and 77°F).

- *Therapy follow-up:*

  Patients receiving tacrolimus as an immunosuppressive treatment should be managed in facilities equipped and staffed with the adequate laboratory and medical staff resources. Physicians with experience in immunosuppressive therapy and transplantation should prescribe and follow tacrolimus therapy. Physicians should be in charge of monitoring tacrolimus therapy and consulted if a patient is converted to another formulation of tacrolimus so that adequate follow-up is ensured.

- *Blood level monitoring in transplant patients:*

  Following transplantation, through blood concentrations should be monitored every 1-3 days. Frequent monitoring is done after transplantation in order to reduce the risk of acute graft rejection. Following discharge from the hospital, the frequency of monitoring will decrease with time. However, patients with renal or hepatic impairment might need more intensive follow-up and close monitoring as tacrolimus levels can be further affected by these conditions. Blood concentration monitoring does not replace necessary liver and renal monitoring. Samples are analyzed following 2 methods: micro-particle enzyme immune assay (MEIA) and enzyme linked immune sorbent assay (ELISA). When samples cannot be analyzed immediately, they must be stored in a refrigerator and analyzed within 3 days. If kept longer, they should be frozen at a temperature of -20 degrees Celsius up to 12 months.

- *Laboratory tests:*

  Serum creatinine, fasting glucose and potassium should be assessed regularly during treatment with tacrolimus.

5. Alternatives to Tacrolimus Available in the Strategic Fund

The current version of the Strategic Fund medicine list includes cyclosporine as an alternative calcineurin inhibitor immunosuppressant. Cyclosporine is also listed on WHO Essential Medicine List.

The following document provides the supporting evidence regarding the comparison of tacrolimus and cyclosporine in the treatment of adult kidney, liver, bone marrow and stem cell, and heart transplant. This document does not represent a therapeutic guideline for treatment of these conditions and it is not intended for such use.

6. Guidelines Including the Use of the Medicine in Relation with the Proposed Indications

Below are presented some of the available guidelines related to organ transplantation.

- The Transplantation Society: KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients - 2009 http://www.tts.org/index.php?option=com_content&view=article&id=642&Itemid=246
- National Institute for Clinical Excellence (NICE): Immunosuppressive Therapy for Renal Transplantation in Adults - 2004 http://www.nice.org.uk/nicemedia/live/11544/32940/32940.pdf
- The International Society of Heart and Lung Transplantation Guidelines for the Care of Heart Transplant Recipients - 2010 http://download.journals.elsevierhealth.com/pdfs/journals/1053-2498/PIIS105324981000358X.pdf

7. Intervention and Summary of Evidence

The clinical questions presented below are based on the PAHO technical unit (HSS/MT) request to incorporate tacrolimus in the Strategic Fund medicine list and input received from three Member States. The evidence presented in this section was obtained in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb).

The intervention and evidence summary has been compiled in four tables (*7.1-7.4*), with the corresponding Grading of Recommendations Assessment, Development and Evaluation (GRADE), and when relevant additional tables.

The evidence presented for use in kidney, liver and heart transplants (*Tables 7.1-7.3*) is supported by systematic reviews. Due to the absence of a systematic review for bone marrow and stem cell transplants (*Table 7.4*), the evidence presented is supported by a critical review of 3 clinical trials.

The search strategy and references supporting the intervention and summary of evidence for all three tables are available in *Section 9* of this dossier.

7.1 Tacrolimus Compared to Cyclosporine for Kidney Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of tacrolimus compared to cyclosporine in the treatment of adult kidney transplant?

CONTEXT	Tacrolimus versus cyclosporine
Over the last past decades, renal transplantation has become established as the treatment of choice for many patients with end-stage renal failure, where the unique alternative is dialysis. The establishment of transplantation has been made possible by the introduction of immunosuppressants. Immunosuppression is usually constituted by a triple therapy containing: i) a calcineurin inhibitor (i.e., ciclosporin); ii) an antiproliferative agent (i.e., azathioprine); and iii) a corticosteroid. People who undergo renal transplantation are required to receive life-long (or at least, long-term) treatment with immunosuppressive drugs. When selecting these treatments, the risk of immunologically mediated graft failure for any donor–recipient pair needs to be balanced against the drug's side effects for the recipient. The ultimate aim of treatment is to prolong patient and graft survival.	

CONTEXT	Tacrolimus versus cyclosporine
An appraisal guidance from the National Institute for Clinical Excellence appraisal states that: "Tacrolimus is an alternative to ciclosporin when a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen in renal transplantation for adults. The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for individual people" (*1*). Recently, the All Wales Medicines Strategy Group (AWMSG) reported the following recommendations: "tacrolimus is recommended as an option for restricted use within the National Health Service Wales (NHS Wales) for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients" and "tacrolimus is not recommended for use within NHS Wales for the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients" (*2*).	

INTERVENTION	Tacrolimus versus cyclosporine
Tacrolimus improves graft survival compared to cyclosporine. *High quality evidence.*	
Tacrolimus reduces the risk of acute rejection and steroid-resistant rejection after kidney transplantation compared to cyclosporine. *High quality evidence.*	
Tacrolimus increases the risk of post-transplant diabetes, neurological and gastrointestinal side effects compared to cyclosporine. *High quality evidence.*	

Summary of evidence	
Benefits	We found Cochrane systematic review with the aim of compare the effects of tacrolimus with cyclosporine as primary therapy for kidney transplant recipients that included 30 studies with a total of 4,102 patients (*3*). Six studies (1,127 participants) compared tacrolimus with the original, oil based solution formulation of cyclosporine, and 19 studies (2,744 participants) compared tacrolimus with the microemulsion formulation and we were unable to clarify which formulation was used. The rest of studies did not provide enough details to clarify which formulation was used. Additional baseline immunosuppression varied within studies (in those trials including three comparison groups) and between studies. Three studies varied an antiproliferative agent across three study arms, investigating combinations of tacrolimus (2 trials), and cyclosporine (1 trial) with mycophenolate (MMF) or azathioprine. Azathioprine was used in both tacrolimus and cyclosporine arms in 16 studies and MMF in eight studies. One study used sirolimus, one used mizoribine, one used no antiproliferative and one study did not state which antiproliferative was used. Twelve studies used antibody induction agents. Seventeen studies reported their corticosteroid reducing regimen in detail, and the remaining 14 studies described "local protocol" or "a standard reducing schedules". Although most studies reported limited information on the study population demographics, the majority were restricted to unsensitized participants with low baseline risk for transplantation. Only two studies included participants with panel reactive antibodies (PRA) > 50% and nine studies included a proportion (range 10-25%) of participants who had previously had a failed renal transplant. The review showed that that at six months graft loss was significantly reduced in tacrolimus-treated recipients (7 RCT, 1,552 patients; RR 0.56, 95% CI 0.36 to 0.86), and this effect was persistent up to three years (7 RCT, 1,513 patients; RR 0.71, 95% CI 0.52 to 0.96). Meta-regression showed that this benefit diminished as higher trough levels of tacrolimus were targeted (P = 0.04), after allowing for differences in cyclosporine formulation (P= 0.97) and cyclosporine target trough level (P = 0.38). At one year, tacrolimus patients suffered less acute rejection (14 RCT, 2,751 patients; RR 0.69, 95% CI 0.60 to 0.79), and less steroid-resistant rejection (9 RCT, 1,770 patients; RR 0.49, 95% CI 0.37 to 0.64).

Summary of evidence	
Risks	The assessed Cochrane systematic review (*3*) highlighted that the included trials that reported disturbance of glucose metabolism used variable definitions. This led the authors to use the most consistent definition used for this outcome, which was the development of new diabetes mellitus, defined as a requirement for insulin therapy for more than 30 days duration. The results of the review showed that at one year, patients treated with tacrolimus that were previously non-diabetic had a greater requirement for insulin for more than 30 days (13 RCT, 2,013 patients; RR 1.86, 1.11 to 3.09), and suffered adverse effects as tremor, headache, diarrhea, dyspepsia or vomiting. Cyclosporine-treated recipients experienced significantly more constipation and cosmetic side-effects. The review did not find differences in the rates of infection or malignancy.
Comments/ Applicability	The assessed Cochrane systematic review (*3*) provides absolute risk per 100 treated recipients with tacrolimus instead of cyclosporine to discuss the applicability of the review results in clinical practice. Based on this analysis, treating a 100 low risk patients (such as adult recipients of well matched, first transplants) with tacrolimus instead of cyclosporine would avoid six acute rejection. This figure would rise to 17 if considering high risk populations (such as sensitised recipients of subsequent grafts). Tacrolimus therapy would avoid one low risk, but three high risk patients losing their grafts. In contrast, treating with tacrolimus would cause an extra five recipients excess harm by rendering them insulin-dependent diabetics. The results from the metaregression performed in the review suggested that when tacrolimus is used, targeting lower trough levels will minimize graft loss and temper the increased risk of diabetes mellitus without increasing the risk of acute rejection. The authors highlighted that in applying this evidence to patients, the choice of calcineurin inhibitor for an individual patient is neither automatic nor straightforward, as risks of benefit and of drawbacks of each therapy must be balanced.
	From the methodological point of view, the authors of the systematic review commented that the quality of data reporting the adverse effects of therapy was less informative than that for the benefits, and adverse effects were inconsistently expressed and grouped (*3*). The majority of studies did not report disturbances of glucose metabolism, or elicit new cases of diabetes that could be controlled by diet or oral hypoglycaemic agents, but used high diagnostic thresholds, recording only those cases requiring sustained insulin therapy. In addition, often the prevalent rather than incident cases were reported, with no indication of the numbers of patients with diabetes prior to transplantation. Both these aspects introduced bias, and would contribute to the underestimation of the true burden of disturbed glucose metabolism within the post-transplant population
Cost studies	A review of the economic literature found 12 studies of varying quality and complexity (*4*). The studies included in the review compared cyclosporine, azathioprine and a corticosteroid (CAS) with tacrolimus, azathioprine and a corticosteroid (TAS) but only three also evaluated the costs and effects of other possible treatment regimens. A variety of different evaluation frameworks were employed, from single randomised controlled trial-based studies over relatively short-time periods (6 months) to more complex Bayesian modeling approaches. The studies were broadly consistent in concluding that TAS was more effective than CAS in terms of reducing the rate of acute rejection episodes. Of the studies that undertook decision modeling, all but one estimated that TAS was associated with better graft-related outcomes such as rejection-free life-years, patient-survival and QALYs. Six of the studies concluded that the healthcare costs associated with TAS were lower than those for CAS. A seventh study suggested that TAS was the least costly option if costs were considered over a relatively long time period (14 years). Only one study clearly concluded that CAS was more cost effective than TAS. The authors highlighted that the evidence shows that TAS is more effective than CAS in terms of reducing the incidence of acute rejection following renal transplantation. The majority of published economic evaluations suggest that TAS is also the more cost-effective option. However, the economic evaluations contained a number of methodological limitations, undermining the confidence that can be attached to their results.

Table 1. GRADE Evaluation of Clinical Outcomes: Tacrolimus Versus Cyclosporine for Kidney Transplant Recipients (Assessment from Data in Reference *3*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
7 (1552)	Six months graft loss	Tacrolimus Cyclosporine	4	0	0	0	0	High	
14 (2751)	Acute rejection at one year	Tacrolimus Cyclosporine	4	0	0	0	0	High	
9 (1770)	Steroid-resistant rejection at one year	Tacrolimus Cyclosporine	4	0	0	0	0	High	
12 (2013)	Requirement for insulin >30 days in previously non-diabetic patients at one year	Tacrolimus Cyclosporine	4	0	0	0	0	High	
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

7.2 Tacrolimus Compared to Cyclosporine for Liver Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of tacrolimus compared to cyclosporine in the treatment of adult liver transplant

CONTEXT	Tacrolimus versus cyclosporine
Liver transplantations are considered a treatment option for any patient with an acute or chronic liver disease that leads to life-threatening complications and a survival prognosis of one year or less. Indications for liver transplantation have evolved to include previously contraindicated conditions such as hepatocellular carcinoma and alcohol-related liver disease. Cirrhosis from chronic hepatitis C infection remains the most common indication today for liver transplantation. In the United States, 6,069 livers were transplanted during 2008 (*1*). People who undergo transplantation are required to receive treatment with immunosuppressive drugs. The All Wales Medicines Strategy Group (AWMSG) reported recently the following recommendations (*2*): "tacrolimus is recommended as an option for restricted use within the National Health Service Wales (NHS Wales) for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients", and "tacrolimus is not recommended for use within NHS Wales for the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients."	

INTERVENTION	Tacrolimus versus cyclosporine
Tacrolimus reduces the risk of mortality compared to cyclosporine. *High quality evidence.*	
Tacrolimus improves graft survival compared to cyclosporine. *High quality evidence.*	
Tacrolimus reduces the risk of acute rejection and steroid resistant rejection after liver transplantation compared to cyclosporine. *High quality evidence.*	

INTERVENTION	Tacrolimus versus cyclosporine
Tacrolimus increases the risk of post-transplant diabetes compared to cyclosporine. *High quality evidence.*	

Summary of evidence	
Benefits	We found Cochrane systematic review with the aim of evaluate the beneficial and harmful effects of immunosuppression with cyclosporine versus tacrolimus for liver transplanted patients that included 16 studies with a total of 3,813 patients (*3*). Most of the trials included restricted enrolment to adults, with the exception of one that included children and one additional that was restricted to children. Hepatitis C virus (HCV) cirrhosis was the commonest indication for transplantation; two randomised trials confined entry to patients with HCV; and only one other trial identified the outcome in patients with HCV. The earliest trials (1,157 participants) compared tacrolimus with the original oil based formulation of cyclosporine whereas the rest of trials (1,656 participants) compared tacrolimus with the microemulsion formulation. In all the included trials the participants received concomitant immunosuppression including corticosteroids (15 trials); azathioprine (4 trials), and mycophenolate mofetil (3 trials). All of the trials used trough level monitoring to guide cyclosporine and tacrolimus dosing except one trial which used the two hour post-dose level to guide the dose of cyclosporine. Data registered from the included trials accounted for 254 deaths in the tacrolimus group (1,899 patients) compared to 302 deaths in the cyclosporine group (1,914 patients). This resulted in a 15% reduction in the mortality at one year in the tacrolimus patients (16 RCT, 3,813 patients; RR 0.85, 95% CI 0.73 to 0.99). Graft survival was reported in 15 trials, showing a 22% relative reduction favoring tacrolimus compared to cyclosporine (16 RCT, 3,813 patients; RR 0.78, 95% CI 0.68 to 0.89). Acute rejection and steroid resistant rejection were reduced by 18% and 43%, respectively, in the tacrolimus treated recipients (16 RCT, 3,786 patients; RR 0.82, 95% CI 0.77 to 0.88; and 11 RCT, 2,439 patients; RR 0.57, 95% CI 0.46 to 0.71).
Risks	The assessed Cochrane systematic review (*3*) showed that substantially more patients discontinued cyclosporine than tacrolimus (16 RCT; 3,813 patients; RR 0.65, 95% CI 0.57 to 0.74). However, the rate of new-onset diabetes was increased by 27% in the tacrolimus treated patients (11 RCT; 3,023 patients; RR 1.27, 95% CI 1.12 to 1.44). No differences were seen in the rates of chronic renal failure requiring dialysis (4 RCT; 344 patients; RR 1.55, 95% CI 0.64 to 3.78) or of those patients with a lymphoproliferative disorder after liver transplantation (7 RCT; 1,107 patients; RR 1.01, 95% CI 0.36 to 2.86).
Comments/ Applicability	The assessed Cochrane systematic review (*3*) provides absolute risk per 100 treated recipients with tacrolimus instead of cyclosporine to discuss the applicability of the review results in clinical practice. Based on this analysis, treating 100 recipients with tacrolimus instead of cyclosporine would avoid acute rejection in nine patients and steroid-resistant rejection in seven patients. Graft loss and death would be avoided in five and two patients, respectively. The treatment with tacrolimus instead of cyclosporine, however, would result in four additional with new-onset diabetes after liver transplantation.

Summary of evidence	
Cost studies	A CRD assessed economic evaluation (*4*) synthesized an economic evaluation (*5*), published in 2001, that compared tacrolimus with cyclosporine following liver transplantation. It was developed in the context of an open label, single-center, prospective clinical trial in the USA which included 60 patients that were followed for 6 months after transplantation. No randomization was performed. The perspective adopted in the study was not stated, but it is likely to have been that of the hospital. The unit costs were reported for drug use. The costs and the quantities were treated deterministically and no sensitivity analyses were conducted. The source of the cost data was not stated, and details of the cost analysis were lacking. The estimated total cost per day of calcineurin inhibitors was US$ 13.69 per day for the tacrolimus group and US$ 27.17 per day for the cyclosporine group. In this study, tacrolimus as a primary immunosuppressant in liver transplantation overall was found to be superior to cyclosporine with a decrease in the number of acute rejections, use of anti-lymphocyte antibodies and estimated total cost of transplantation at 6 months post-transplantation. The authors made several comparisons of their findings with those from other studies. However, they did not address the issue of the generalizability of the study results to other settings. Sensitivity analyses were not conducted, thus the external validity of the analysis is relatively low (*4*).

Table 1. GRADE Evaluation of Clinical Outcomes: Tacrolimus Versus Cyclosporine for Liver Transplant Recipients (Assessment from Data in Reference *3*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
16 (3813)	Mortality	Tacrolimus Cyclosporine	4	0	0	0	0	High	
16 (3813)	Graft loss	Tacrolimus Cyclosporine	4	0	0	0	0	High	
16 (3813)	Acute rejection	Tacrolimus Cyclosporine	4	0	0	0	0	High	
11 (2439)	Steroid-resistant rejection	Tacrolimus Cyclosporine	4	0	0	0	0	High	
5 (873)	Dialysis (de-novo requirement post-transplantation)	Tacrolimus Cyclosporine	4	0	0	0	0	High	
11 (3023)	New-onset diabetes mellitus	Tacrolimus Cyclosporine	4	0	0	0	0	High	
7 (1107)	Post transplant lymphoproliferative disease	Tacrolimus Cyclosporine	4	0	0	0	0	High	
13 (3156)	Patients withdrawn from tacrolimus or cyclosporine	Tacrolimus Cyclosporine	4	0	0	0	0	High	
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

7.3 Tacrolimus Compared to Cyclosporine for Heart Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of tacrolimus compared to cyclosporine in the treatment of adult heart transplant?

CONTEXT	Tacrolimus versus cyclosporine

Heart transplantation is an established treatment option, and often the only long term treatment alternative, for end-stage heart failure in selected patients. To date more than 85,000 heart transplantations have been reported worldwide to the International Society for Heart and Lung Transplantation (ISHLT) (*1*). More than 5000 heart transplantations are performed annually with a one-year survival over 85% and a five-year survival over 75% (*1,2*).

Immunosuppression medication is paramount to long term survival. Due to immunological rejection of the new heart, heart transplant recipients are at risk of significant morbidity and mortality (*3*). Up to 97% of surviving recipients have hypertension, 93% have hyperlipidemia, 52% have angiographic chronic allograft vasculopathy, 39% have diabetes mellitus and 14% have severe renal insufficiency (*1*).

To reduce morbidity and increase survival it is essential to find the most optimal immunosuppressive treatment strategy. Cyclosporine was the first calcineurin inhibitor to become available for clinical use in transplantation in the early 1980s. A microemulsion formula of cyclosporine was introduced in the 1990s to overcome the intra-individual and inter-individual differences in absorption and the bioavailability of the original oil-based formulation. Since tacrolimus was used from 1989 for the prevention of liver transplant rejection, its use expanded rapidly into the transplantation of other organs. Both drugs inhibit the action of the phosphatase calcineurin. Differences between cyclosporine and tacrolimus with regard to adverse effects, safety, and tolerability have been observed, but the toxicodynamic molecular mechanism of both drugs is still largely unknown and the involvement of calcineurin inhibition in calcineurin inhibitor toxicity is unclear (*4*).

Therefore, the optimal immunosuppressive maintenance therapy continues to be debated, due to inconsistent results from published trials to date.

INTERVENTION	Tacrolimus versus cyclosporine
Tacrolimus does not show differences in mortality compared to cyclosporine. *Moderate quality evidence.*	
Tacrolimus does not show differences in Grade 3 A or higher rejection compared to cyclosporine. *Moderate quality evidence.*	
Tacrolimus reduces the risk of Grade 3 A or higher rejection compared with microemulsion cyclosporine. *Moderate quality evidence.*	
Tacrolimus does not show differences in rejection causing haemodynamic instability compared to microemulsion cyclosporine. *Moderate quality evidence.*	
Tacrolimus reduces the risk of hypertension or the requirement on medication to treat hyperlipidaemia, and reduces the cholesterol level compared with cyclosporine. *Low quality evidence.*	
Tacrolimus increases the risk of post-transplant diabetes compared with microemulsion cyclosporine. *Low quality evidence.*	
Tacrolimus decreases the risk of hirsutism or gingival hyperplasia compared with microemulsion cyclosporine. *Low quality evidence.*	
Tacrolimus does not show differences in infection, cytomegalovirus, basocellular skin cancer or other malignancies, renal failure requiring haemodialysis, chronic allograft vasculopathy or neurotoxicity compared to cyclosporine. *Low quality evidence.*	

Summary of evidence	
Benefits	A systematic review (10 RCTs) with 14 meta-analyses was found (*4*). The included trials performed head to head comparisons of tacrolimus and cyclosporine after first-time isolated heart transplantation. Eight studies included only adult patients, one both adult and pediatric patients and one included only pediatric patients. All patients only participated once in the trials. The studies enrolled a total of 952 patients (486 in the tacrolimus and 466 in the cyclosporine cohorts) who received a heart transplant. All patients only participated once in the trials. Follow-up ranged from 6 to 60 months. All trials assessed tacrolimus and cyclosporine combined with a concomitant immunosuppressive treatment. No detailed data about doses were provided. All patients were treated with steroids. All trials had a high risk of bias. Methodology was inadequately reported and trials were unblinded, except one where blinding was unclear. Only 2 RCTs reported adequate sequence generation and concealment allocation; in most of them these items were unclear. In all but one the analyses were performed according to the intention to treat, and all except two addressed the incomplete outcome data. The trials assessed a series of events related to the transplant (acute rejection, mortality), as well as safety outcomes such as any infection, citomegalovirus (CMV) infection, basocellular skin cancer, all malignancies excluding basocellular skin cancer; arterial hypertension; post-transplant diabetes mellitus; hyperlipidaemia; total serum cholesterol; renal failure requiring hemodialysis; serum creatinine levels; neurotoxicity; hirsutism; and gingival hyperplasia. The results showed that tacrolimus and cyclosporine did not show differences in mortality (10 RCT, 952 patients; RR 0.78; 95%CI 0.54 to 1.13). However, when tacrolimus showed a reduction in the risk of dying compared to microemulsion cyclosporine (7 RCT, 760 patients; RR 0.64; 95% CI 0.42 to 0.96; p = 0.03). No significant difference in mortality was observed between tacrolimus and oil-based cyclosporine (3 RCT, 192 patients; RR 1.79; 95% CI 0.77 to 4.15, p = 0.17). The significant difference in mortality between tacrolimus and microemulsion cyclosporine, disappeared when the studies including pediatric patients were excluded from the analysis (RR 0.66; 95% CI 0.40 to 1.09). A test for interaction showed no differences between results in adult or pediatric patients (p=0.89). Suggesting that the lack of significance after the exclusion of pediatric studies was caused by a reduction in the number of patients and events in the groups compared. The review did not show a difference in the number of patients with 3A or higher rejection when compared tacrolimus and cyclosporine (5 RCT, 700 patients, RR 0.86; 95% CI 0.62 to 1.20). This result showed a moderate heterogeneity (I^2 = 46%). However, tacrolimus was associated with a significant reduction in Grade 3 A or higher rejection compared with microemulsion cyclosporine (4 RCT, 615 patients; RR 0.71; 95% CI 0.56 to 0.90, p=0.004). Rejection causing haemodynamic instability was not significantly different between tacrolimus and microemulsion cyclosporine (5 RCT; RR 0.96; 95% CI 0.34 to 1.38).

Summary of evidence	
Risks	The assessed systematic review (*4*) showed a statistically significant reduction of tacrolimus showed a reduction in the number of patients with hypertension compared with cyclosporine (8 trials, 824patients; RR 0.80; 95% CI 0.69 to 0.93, p = 0.003), but this result was affected by a high heterogeneity (I2 = 62%). In both cases, findings were similar regardless the type of cyclosporine used. Fewer patients treated with tacrolimus were treated pharmacologically for hyperlipidaemia compared cyclosporine (4 trials, 431 patients; RR 0.57; 95%CI 0.44 to 0.74; p < 0.0001). The data from 5 trials showed that tacrolimus significantly lowers total cholesterol compared with cyclosporine (5 trials; mean difference [MD] 0.4 mmol/l; 95% CI −0.66 to −0.22 mmol/l, p < 0.0001). In both cases, findings were similar regardless the type of cyclosporine used. Eight trials reporting on the outcome post-transplant diabetes found more incidence of diabetes in tacrolimus compared with cyclosporine group, but such a difference did not reach statistical significance (8 trials, 820 participants; RR 1.35; 95% CI 0.93 to 1.94). In both cases, findings were similar regardless the type of cyclosporine used. However, when the fixed-effect model was applied, tacrolimus showed a significant difference with cyclosporine (RR 1.24; 95% CI 1.02 to 1.49, p = 0.03) and with microemulsion cyclosporine (RR 1.25; 95% CI 1.03 to 1.51, p = 0.02) were found. Hirsutism was significantly less frequent in patients treated with tacrolimus than in those treated with microemulsion cyclosporine (2 trials; RR 0.17; 95% CI 0.04 to 0.62; p = 0.008). Gingival hyperplasia was also significantly less frequent in patients treated with tacrolimus than in those treated with microemulsion cyclosporine (3 trials; RR 0.07; 95% CI 0.01 to 0.37, p = 0.002). On the other hand, the review showed a non-significant difference in number of patients with infection between tacrolimus and cyclosporine (RR 1.01; 95% CI 0.84–1.21). Two trials comparing the number of patients with CMV infection for tacrolimus versus microemulsion cyclosporine found no significant difference between the groups (RR 1.03; 95% CI 0.75 to 1.42). Three trials found no significant difference between tacrolimus and microemulsion cyclosporine for basocellular skin cancer (RR 1.20; 95% CI 0.29 to 4.93), and four trials reported also no statistical significance for other cancers (RR 0.57; 95% CI 0.20 to 1.63). In both cases, findings were similar regardless the type of cyclosporine used. No significant difference between tacrolimus and cyclosporine was observed concerning either renal failure requiring hemodialysis (RR 1.45; 95% CI 0.50 to 4.26), or serum creatinine at the end of the trials (6 trials; 95% CI −18.3 to −1.7 µmol/l). In both cases, findings were similar regardless the type of cyclosporine used. No significant difference was found for tacrolimus compared with cyclosporine regarding chronic allograft vasculopathy (5 trials; RR 1.22; 95% CI 0.72 to 2.05). Findings were similar regardless the type of cyclosporine used. No significant difference was observed according the number of events of neurotoxicity between tacrolimus and cyclosporine (RR 1.31; 95% CI 0.58 to 3.00). Findings were similar regardless the type of cyclosporine used.

Summary of evidence	
Comments/ Applicability	The results of the assessed systematic review (*4*) showed a significant reduction in patients treated with tacrolimus in arterial hypertension, hyperlipidemia, hirsutism and gingival hyperplasia. Subgroup analyses showed that tacrolimus compared to microemulsion cyclosporine reduced mortality (36%) and acute rejection (29%). On the other hand, tacrolimus showed a trend to worse results in terms of incidence of post-transplant diabetes, which was confirmed when a fixed-effect model was used in the analysis. No significant differences were seen in safety outcomes such as infections, malignancies, renal failure, chronic allograft vasculopathy and neurotoxicity. Therefore, the review showed that safety profile is similar with both drugs.
	However, except for mortality and hypertension, the number of events in each comparison was in general small, which make the interpretation of findings difficult, so that the absence of difference in the analyses may result from a lack of statistical power, instead of an apparent similarity between the treatments. Also, in several outcomes the numbers of events were not displayed; therefore, judgments about precision of effect estimates were not possible.
	According to the authors' point of view, most trials included in the review did not include patients who were bridged to transplantation with a left ventricular device, and this type of patient has been increasing in the general heart transplantation population. Another important threat to the external validity of the review is the fact that heart transplant recipients have become older, and currently 25% of all heart transplants performed in people over 60 years of age. Another factor which could influence in the best performance of tacrolimus is that clinical experience with this newer drug was more limited in the trials comparing it with oil-based cyclosporine, as well as the higher tacrolimus blood target levels achieved in the trials with oil-based cyclosporine.
	Another weakness of this review is the poor quality of the included studies, since all the trials were judged as having high of bias, and only two of them reported adequate sequence generation and allocation concealment.
	The applicability of these results should be considered in the light of the issues related to their validity, due to the poor methodological quality of the trials, the small number of events in some outcomes, and the lack of data to make appropriate judgments about the quality of evidence. Another point is that one of the formulations compared is not the preparation currently marketed.
Cost studies	The search did not retrieved relevant economic evaluations assessing the cost-effectiveness of tacrolimus and cyclosporine in heart transplantation.

Table 1. GRADE Evaluation of Clinical Outcomes: Tacrolimus Versus Cyclosporine for Heart Recipients (Assessment from Data in Reference *4*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
10 (952)	Mortality	Tacrolimus Cyclosporine	4	-1	0	0	-1	Low	Methodology inadequately reported. Trials unblinded, or blinding unclear. Sequence generation and concealment allocation unclear. Few events in each group.
5 (700)	Acute rejection	Tacrolimus Cyclosporine	4	-1	0	0	0	Moderate	Methodology inadequately reported. Trials unblinded, or blinding unclear. Sequence generation and concealment allocation unclear.
8 (824)	Arterial hypertension	Tacrolimus Cyclosporine	4	-1	-1	0	0	Moderate	Methodology inadequately reported. Trials unblinded, or blinding unclear. Sequence generation and concealment allocation unclear. Significant heterogeneity.
4 (431)	Hyperlipidemia	Tacrolimus Cyclosporine	4	-1	0	0	-1	Low	Methodology inadequately reported. Trials unblinded, or blinding unclear. Sequence generation and concealment allocation unclear. Few events in each group.
8 (820)	Post-transplant diabetes	Tacrolimus Cyclosporine	4	-1	-1º	0	0	Low	Methodology inadequately reported. Trials unblinded, or blinding unclear. Sequence generation and concealment allocation unclear. Inconsistent results depending of the effect model used in the analysis
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

7.4 Tacrolimus Compared to Cyclosporine for Bone Marrow and Stem Cell Transplant Recipients

CLINICAL QUESTIONS
What is the efficacy and safety of tacrolimus compared to cyclosporine in the treatment of adult bone marrow and stem cell transplant?

CONTEXT	Tacrolimus versus cyclosporine

The hematopoietic stem cell transplantation (HSCT) technique has a curative effect on patients with hematological malignancies by means of the high dose of cytotoxic drugs and total body irradiation (TBI) used in the conditioning regimen before transplantation, which destroys the donor's immune system and most of the remnant tumor cells. Moreover, with the reconstitution of the immune system (*1*), the graft versus leukemia or lymphoma (GVL) effects eradicate the residual malignant cells (*2*).

However, graft versus host disease (GVHD) remains as the major complication following allogeneic HSCT that limits wide use of HSCT. GVHD is the disease that occurs after transplantation of allogeneic stem cells, characterized by impairment of recipient's organs including skin, intestine, liver and lung (*3,4*). It has been proposed that the pathogenesis of GVHD includes the three considerations of administration of an immunocompetent graft, histoincompatibility between donor and recipient, and that the recipient is immunocompromised and therefore cannot destroy or inactivate the transplanted immune cells (*5*). GVHD accounts for 10% of deaths in HLA matched sibling HSCT and 12% of deaths in unrelated donor HSCT. Furthermore, immunosuppressants used to prevent and treat GVHD add to the risk of infection, which is the highest ranking non-primary disease causing death.

GVHD is classified into acute and chronic forms, and both of these two types contribute to poor prognosis following HSCT. The recent definition of acute or chronic GVHD proposed by the National Institutes of Health (NIH) Consensus Conference is based on the specificity of signs and symptoms rather than the time of onset (*6*). The incidence of clinically significant grade II to IV aGVHD is 35% to 40% in matched sibling donor groups, and 40% to more than 50% in unrelated donor groups (*7*). Depending on the risk group, the incidence of clinically significant aGVHD could range from no more than 10% to as high as 80% (*8*). Although aGVHD is a favorable factor to predict GVL effect and reduced relapse, grade II-IV aGVHD accounts for both early death and poor long-term survival following a transplant; and in patient with grade IV aGVHD the mortality within 100 days post-transplant and treatment-related mortality can be as high as 70% to 92% (*9*).

Cyclosporine was the first calcineurin inhibitor to become available for clinical use in transplantation in the early 1980s. A microemulsion formula of cyclosporine was introduced in the 1990s to overcome the intra-individual and inter-individual differences in absorption and the bioavailability of the original oil-based formulation. Since tacrolimus was used from 1989 for the prevention of liver transplant rejection, its use expanded rapidly into the transplantation of other organs. Both drugs inhibit the action of the phosphatase calcineurin. Differences between cyclosporine and tacrolimus with regard to adverse effects, safety, and tolerability have been observed, but the toxicodynamic molecular mechanism of both drugs is still largely unknown and the involvement of calcineurin inhibition in calcineurin inhibitor toxicity is unclear (*10*).

INTERVENTION	Tacrolimus versus cyclosporine
Tacrolimus reduces the risk of grade II-IV acute GVHD compared to cyclosporine. *Low quality evidence.*	
Tacrolimus does not show differences in survival, grade III-IV acute GVHD, chronic GVHD, relapse rates or engraftment compared to cyclosporine. *Low quality evidence.*	
Tacrolimus increases the incidence of renal adverse effects compared to cyclosporine. *Low quality evidence.*	

Summary of evidence	
Benefits	We did not identify relevant systematic reviews for this clinical question, but a specific search of trials retrieved 3 relevant RCT (*11-13*). The trials by Ratanatharathorn (*11*) and Nash (*12*) were two phase III open-label, randomized, multicenter trials comparing the combination of tacrolimus and methotrexate to cyclosporine and methotrexate for graft-versus-host disease prophylaxis. Ratanatharathorn explored the effect of treatment after HLA-identical sibling marrow transplantation in patients with hematologic malignancy (*11*), whilst in Nash the marrow transplantation came from unrelated donors (*12*). In the remaining study Hiraoka (*13*) reported the results of a phase III study that compared tacrolimus with cyclosporine for graft-versus-host disease prophylaxis after allogeneic bone marrow transplantation. Ratanatharathorn included 329 patients (136 women, 193 men), 165 patients were randomized to receive tacrolimus (72 women, 93 men) and 164 patients were randomized to receive cyclosporine (64 women, 100 men) (*11*). With the exception of the stage of malignancy (more patients with non advanced disease in the cyclosporine group), groups were comparable with respect to age, gender, Karnofsky performance status, ethnicity, positive serology for cytomegalovirus and diagnosis. Nash enrolled 180 patients (82 women, 98 men), 90 patients randomized to receive tacrolimus (44 women, 46 men) and 90 patients to receive cyclosporine (38 women, 52 men). With the exception of the HLS status, where HLA class II antigen mismatches were more frequent in the cyclosporine group than in the tacrolimus group, groups were comparable with respect to age, gender, cytomegalovirus, diagnosis and conditioning regimen (*12*). In both studies, the starting dose was 0.03 mg/kg/d for tacrolimus and 3 mg/kg/d for cyclosporine, and was modified according primarily to the serum creatinine and the blood levels of tacrolimus or cyclosporine. Hiraoka enrolled 131 patients (54 women, 77 men), 66 randomized to receive tacrolimus (24 women, 42 men) and 65 to receive cyclosporine (30 women, 35 men) (13). Groups were comparable with respect to age, donor–recipient relation, and underlying disease and disease status. The starting dose of tacrolimus was either 0.075 mg/kg. No data were provided on the cyclosporine regimen. The Table 1 outlines the main characteristics of the studies considered. Ratanatharathorn assessed a series of events related to the efficacy and safety of tacrolimus/methotrexate versus cyclosporine/methotrexate, such as acute GVHD, chronic GVHD, survival and relapse, engraftment, and toxicities (*11*). Nash assessed outcomes such as acute GVHD, chronic GVHD, survival, relapse, engraftment, and adverse events (*12*). Hiraoka assessed outcomes such as acute GVHD, engraftment, and adverse drug reactions (*13*). Ratanatharathorn (*11*) showed that tacrolimus/methotrexate compared to cyclosporine/methotrexate significantly reduced the incidence of grade II-IV acute GVHD (-31.9% versus 44.4%) with an absolute difference of 12.5% (95%CI 1.2 to 23.9; p=0.01). However, the incidence of grade III-IV acute GVHD was similar, 17.1% with cyclosporine and 13.3% with tacrolimus. For the outcome chronic GVHD, at 2 years of follow up, there was no difference between the tacrolimus and the cyclosporine groups (-55.9% versus 49.4%; p=0.8). There was a significantly higher proportion of patients in the cyclosporine group with clinical extensive disease (p = 0.03). The study found significant differences for survival favoring the cyclosporine group, with a significantly better survival compared to patients who received tacrolimus (2-year survival rates 57.2% with cyclosporine and 46.9% with tacrolimus; absolute difference 10.3%; 95% CI -21.1 to 0.5; p = 0.02). However, the advantage in the overall survival was limited to the patients with advanced disease, 24.8% in the tacrolimus group and 41.7% in the cyclosporine group, respectively (absolute difference 16.9%; 95% CI -34.3 to 0.4; p = 0.006). No differences were detected either in the survival rates in patients with non advanced disease (62.4% in the tacrolimus group versus 63.6% in the cyclosporine group; absolute difference 1.2%; 95% CI -14.4 to 11.9; p = 0.79), or in the causes of death in patients with non advanced disease. However, in the patients with advanced disease, there was a higher frequency of deaths from GVHD in patients who received cyclosporine (p = 0.06), and from regimen-related toxicity in patients who received tacrolimus (p = 0.04). There was no difference in relapse rates between patients who received tacrolimus (24.8%; 95% CI 18.2 to 31.4) and patients who received cyclosporine (22.0%; 95% CI 15.7 to 28.3) (p = 0.54). Regarding engraftment, the median times to the recovery of absolute neutrophil counts >= 0.5 x 109/l did not differ between the groups (tacrolimus 19 days versus cyclosporine 20 days; p = 0.78).

Summary of evidence	
Benefits *(cont.)*	Nash 2000 (*12*) showed that the incidence of grade II-IV acute GVHD according to Kaplan-Meier estimates, was 56% (n = 46) in the tacrolimus-treated group and 74% (n = 63) in the cyclosporine-treated group (p = 0.0002). There was no treatment by center interaction for the overall incidence of acute GVHD (p = 0.80). There was also no difference in the incidence of acute GVHD among subgroups of patients classified by age, use of total body irradiation, or HLA match. For the outcome chronic GVHD, a minimum 2-year follow-up after transplantation revealed no significant differences in the overall incidence based on Kaplan-Meier estimates or severity of chronic GVHD between the treatment groups (tacrolimus, 43/69 patients [76%]; CSP, 38/63 patients [70%]; p = 0.88). Ten patients in the tacrolimus group and three in the CSP group had de novo onset of chronic GVHD. Regarding survival, the Kaplan-Meier estimate of relapse-free survival at 2 years after transplantation was 47% in the tacrolimus group and 42% in the cyclosporine group (p = 0.57). Overall survival rates at 2 years were 54% in the tacrolimus group and 50% in the cyclosporine group (p = 0.46). Causes of death were similar between the groups, being the most common, graft failure, relapse, regimen related toxicity and infections. No difference was found in non relapse mortality rates were in the tacrolimus and cyclosporine groups (33% and 42%, respectively; p = 0.24). The study showed that 18 patients (20%) and 14 patients (15.6%) had relapses in the tacrolimus and the cyclosporine groups, respectively. Minimum follow-up was 2 years. Median times to relapse were 127 days (range, 53-700 days) and 162 days (range, 75-655 days) from transplantation for the tacrolimus and cyclosporine groups, respectively. No differences between interventions were detected regarding engraftment (82 patients [91%] in the tacrolimus group and 77 patients [86%] in the cyclosporine group), and neither for the median time to neutrophil engraftment (21 days [range 12-41 days] for patients in the tacrolimus group and 20 days [range 11-34 days] for patients in the cyclosporine group). By 6 months after transplantation, platelet transfusion independence occurred in 50 patients (56%) in the tacrolimus group and 42 patients (47%) in the cyclosporine group. The results of Hiraoka 2001 showed that the cumulative incidence of grade II–IV acute GVHD during the first 100 days after transplantation in the tacrolimus and cyclosporine groups were 17.5% and 48.0%, respectively (p<0.0001). The cumulative incidence of grade III–IV acute GVHD was 9.5% in the tacrolimus group and 21.1% in the cyclosporine group (p = 0.07). For the outcome engraftment, there was no statistical difference between the two treatment groups with respect to the cumulative incidence rate of restoration of bone marrow function 100 days after transplantation, assessed by WBC (p = 0.48), neutrophil (p = 0.90); and platelet (p = 0.60). No differences were observed in the cumulative incidence of chronic GVHD (47.3% in the tacrolimus versus 47.8% in the cyclosporine group; p = 0.77), the cumulative survival rate (62.9% in the tacrolimus group versus 65.2% in the cyclosporine group; p = 0.93), or the cumulative relapse rate (19.6% in the tacrolimus group versus 11.4% in the cyclosporine group; p = 0.30).In a subgroup analyses, relapse rate was significantly higher in the tacrolimus group (30.9%) compared with the cyclosporine group (3.6%, p = 0.013) among recipients from HLA-matched siblings.
Risks	Ratanatharathorn (*11*) obtained data on the incidence of renal toxicity, veno-occlusive disease of the liver and hyperglycemic events. The incidence of serum creatinine increasing above 2 mg/dl within 8 weeks of transplantation was significantly higher in the tacrolimus group (p =0.03) but was not different from the cyclosporine arm at 26 weeks (p = 0.16). The incidence of renal failure requiring hemodialysis was significantly higher in the tacrolimus group, of which the patients with advanced disease accounted for most of the events and the difference between treatment groups. The incidence of hyperglycemia requiring insulin within 8 weeks of transplantation was significantly higher in the tacrolimus group but was not different at 26 weeks. The incidence of hypertension requiring antihypertensive medications was significantly higher in the cyclosporine group (p= 0 .001). The incidence of veno-occlusive disease and neurologic side effects were similar in both groups. Nash 2000 considered the following adverse effects of the drugs studied: nephrotoxicity, serum bilirubin concentrations, veno-occlusive disease, hypertension, hyperglycemia requiring treatment, neurologic side effects, hypokalemia or hypomagnesaemia, and infection (*12*). Differences were observed only for kidney-related adverse effects, specifically for serum creatinine greater than 2 mg/dl, which was greater in the tacrolimus group (p = 0.037). For the rest of outcomes, no statistically significant differences were detected.

Summary of evidence	
Risks	In Hiraoka 2001, no significant differences were observed in adverse drug reactions (31.3% in the tacrolimus group, 18.2% in the cyclosporine group; p = 0.12) (*13*). The major adverse drug reactions encountered were hypertension, numbness and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura syndrome in the tacrolimus group and hypertension in the cyclosporine group. Abnormal laboratory test findings were obtained in 68.7% of the patients in the tacrolimus group and in 47.0% of the patients in the cyclosporine group (p = 0.018). The most frequently reported abnormal laboratory test findings involved renal function parameters, hyperkalemia, abnormal glucose tolerance and hypomagnesaemia. No patient required hemodialysis. Within 100 days post-transplant, study drug was discontinued in 27 patients in the tacrolimus group and 25 patients in the cyclosporine group. The main reasons for discontinuation were adverse drug reactions and abnormal laboratory test findings in the tacrolimus group (n = 14), and progression of acute GVHD in the cyclosporine group (n = 10).
Comments/ Applicability	The overall results from the considered trials (*11-13*) showed a significant benefit with tacrolimus compared to cyclosporine in reducing the incidence of grade II-IV acute GVDH, which was consistent through the three included studies. Regarding survival, results are inconsistent, ranging from a better performance of cyclosporine in one study, to lack of difference in two trials. Therefore, no firm conclusions can be drawn from these data regarding the risk of mortality. Both treatments showed similar efficacy for other important outcomes such as grade III-IV acute GVDH and chronic GVDH, relapse rates and engraftment.
	However, the adverse effects profile was clearly more favourable to cyclosporine, being the kidney-related events the most commonly recorded in the studies, such as renal failure and increased levels of creatinine. Nonetheless, data should be interpreted with caution because of the small number of events in each group, so that the absence of difference in the analyses may result from a lack of statistical power, instead of an apparent similarity between the treatments.
	According to the author´s point of view, the nephrotoxicity of tacrolimus may be related to whole blood concentrations of tacrolimus above 20ng/ml. Therefore, further studies to define the drug levels to minimize toxicity while preserving a high level of immunosuppressive effect of this agent are crucial to optimize its therapeutic profile.
	A limitation for the studies included in this clinical question is the fact that only three trials were included, and that such trials were not homogeneous in terms of the patients included and combination of drugs used. Thus, it is not possible to make a pooled estimation of the effect of the interventions, which preclude from making a reliable judgment about the quality of the evidence.
	The applicability of these results is limited due to the limited number of trials, participants and events in the analyses. The results of this review suggest that tacrolimus has a better efficacy in terms of reducing the incidence of grade II-IV acute GVDH, but such merit is diminished by a less favourable adverse effects profile, mainly related to nephrotoxicity. Therefore, randomized controlled studies are needed to optimize the therapeutic doses.
Cost studies	The search did not retrieved relevant economic evaluations assessing the cost-effectiveness of tacrolimus and cyclosporine in stem cell transplant recipients.

Table 1. Characteristics of Included Studies

Study ID	Design (Sample size)	Patients	Intervention	Outcomes
Ratanatharathorn 1998 (*11*)	Phase III open-label, randomized, multicenter trial. 329 patients (136 women, 193 men), 165 patients were randomized to receive tacrolimus (72 women, 93 men) and 164 patients were randomized to receive cyclosporine (64 women, 100 men).	Patients age of 12 years of age or older, with hematologic malignancy receiving a HLA-identical sibling marrow transplantation. With the exception of the stage of malignancy (more patients with non advanced disease in the cyclosporine group), groups were comparable with respect to age, gender, Karnofsky performance status, ethnicity, positive serology for cytomegalovirus and diagnosis.	Tacrolimus/methotrexate versus cyclosporine/ Methotrexate. The starting dose was 0.03 mg/kg/d for tacrolimus and 3 mg/kg/d for cyclosporine, and was modified according primarily to the serum creatinine and the blood levels of tacrolimus or cyclosporine.	**Primary** Acute GVDH Chronic GVDH **Secondary** Relapse rates Engraftment Adverse effects
Nash 2000 (*12*)	Phase III open-label, randomized, multicenter trial. 180 patients (82 women, 98 men), 90 patients were randomized to receive tacrolimus (44 women, 46 men) and 90 patients were randomized to receive cyclosporine (38 women, 52 men).	Patients 12 years of age or older, scheduled to receive a transplantation of unmodified marrow from human leukocyte antigen matched unrelated donors from an unrelated donor for chronic myelogenous leukemia in chronic or accelerated phase, early acute leukemia or malignant lymphoma, aplastic anemia or myelodysplastic syndrome. With the exception of the HLS status, where HLA class II antigen mismatches were more frequent in the cyclosporine group than in the tacrolimus group, groups were comparable with respect to age, gender, cytomegalovirus, diagnosis and conditioning regimen.	Tacrolimus/methotrexate versus cyclosporine/ Methotrexate. The starting dose was 0.03 mg/kg/d for tacrolimus and 3 mg/kg/d for cyclosporine, and was modified according primarily to the serum creatinine and the blood levels of tacrolimus or cyclosporine.	**Primary** Acute GVDH Chronic GVDH **Secondary** Relapse rates Engraftment Adverse effects
Hiraoka 2001 (*13*)	Open-label, randomized, parallel group study. 131 patients (54 women, 77 men), 66 were randomized to receive tacrolimus (24 women, 42 men) and 65 to receive cyclosporine (30 women, 35 men).	Male and female patients who were scheduled for their first T cell-repleted allogeneic bone marrow transplantation. Groups were comparable with respect to age, donor–recipient relation, and underlying disease and disease status.	Tacrolimus versus cyclosporine. The starting dose of tacrolimus was either 0.075 mg/kg. No data were provided on the cyclosporine regimen.	**Primary** Acute GVDH Chronic GVDH **Secondary** Relapse rates Engraftment Adverse effects

Table 2. GRADE Evaluation of Clinical Outcomes: Tacrolimus Versus Cyclosporine for Stem Cell Transplant Recipients (Assessment from Data in References *11-13*)

Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
3 (640)	Grade II-IV acute GVDH	Tacrolimus Cyclosporine	4	-1	0	0	-1	Low	Open-label studies. Clinical heterogeneity. Few events in each group. No Confidence Intervals provided, but only p – values.
3 (640)	Chronic GVDH	Tacrolimus Cyclosporine	4	-1	0	0	-1	Low	Open-label studies. Clinical heterogeneity. Few events in each group. No Confidence Intervals provided, but only p – values.
3 (640)	Relapse rate	Tacrolimus Cyclosporine	4	-1	0	0	-1	Low	Open-label studies. Clinical heterogeneity. Few events in each group. No Confidence Intervals provided, but only p – values.
3 (640)	Engraftment	Tacrolimus Cyclosporine	4	-1	0	0	-1	Low	Open-label studies. Clinical heterogeneity. Few events in each group. No Confidence Intervals provided, but only p – values.
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

8. Special Considerations and Additional Comments *(11-19)*

8.1 Regulatory Status of the Product in National Regulatory Authorities (NRAs)

The following table reflects the regulatory status of the product (originator and non originator – if applicable) in the 7 PAHO Region Reference NRAs (Argentina, Brazil, Canada, Colombia, Cuba, Mexico and United States) and the European Medicine Agency.

NRA	Status					
	0.5 mg Cap		1 mg Cap		5 mg Cap	
	Originator	Non Originator	Originator	Non Originator	Originator	Non Originator
Argentina (ANMAT)	x	x	x	x	x	x
Brazil (ANVISA)	---	---	x	x	x	x
Canada (Health Canada)	x	---	x	---	x	---
Colombia (INVIMA)	---	---	x	x	x	x
Cuba (CECMED)	---	---	---	x	---	---
Mexico (COFEPRIS)	x	x	x	x	x	x
USA (FDA)	x	x	x	x	x	x
Europe (EMA)	x	---	x	---	x	---

8.2 PAHO Member State Prices

Through ECONMED (an electronic listserv for public officials from the health sector), PAHO requested the price paid for procurement of tacrolimus from Member States who utilize this products in their National Public Health Programs. Unfortunately, no data has been provided to PAHO by countries in Latin America and the Caribbean. PAHO will increase efforts to obtain some prices from Member States and will distribute the information when the committee convenes in Washington, D.C.

8.3 Results of PAHO Expression of Interest

For a medicine to be eligible for inclusion in the PAHO Strategic Fund medicine list, it must have supporting evidence of safety, efficacy, and clinical effectiveness. Additionally the product must satisfy one of the following criteria as related to the pharmaceutical market:

1. The acquisition of the medicines is subject to particular challenges related to product procurement, pricing, patent status, forecasting of future needs, and exclusivity contracts between pharmaceutical companies that restrict marketing in specific geographical areas.
2. Leveraging economies of scale (increases in the volume of medicine procured) can result in lower costs.

PAHO has established this criteria to ensure the inclusion of the product in the Strategic Fund will provide value added to Member States who procure this product through PAHO.

To evaluate these pharmaceutical market factors, the Procurement (PRO) Unit of PAHO conducted an Expression of Interest (EoI) to gather information related to the product. PRO contacted 19 suppliers, which are included in the PAHO approved supplier list, and asked for product data (i.e. available presentations, manufacturing origin & capacity, potential restrictions, prices, and available technical documents).

Limited response was obtained from the contacted suppliers; however, PRO believes tacrolimus, does meet the pharmaceutical market criteria. Nonetheless, significant challenges are present and the following are key recommendations:

- Consolidate regional demand to leverage the benefits of economies of scale. If PAHO is able to obtain sufficient demand perform an international tender and establish Long Term Agreements with suppliers.
- Increase number of PAHO approved suppliers offering this product in order to ensure availability and create a more competitive market.

8.4 Potential Value Added for Procurement of the Medicine through the Strategic Fund

The current version of the Strategic Fund medicine list, published in April of 2013, may limit options in treatment of patients receiving transplants, as the Fund offers two immunosuppressive medicines (azathioprine & cyclosporine) and of these two, only cyclosporine is a calcineurin inhibitor. If the presented evidence demonstrates adequate safety, efficacy, and clinical effectiveness, PAHO believes the inclusion of this product will improve Member States access to an effective and safe medicine that can be used to improve graft and patient survival in post-transplant therapy.

Reference pricing for tacrolimus was not readily available; however, anecdotal data does indicate tacrolimus is expensive in comparison to other immunosuppressive medicines. If included in the Strategic Fund List, PAHO would aim to consolidate regional demand to lower the costs of the product, thus easing the financial burden on Member States.

9. Search Strategy and References Supporting Intervention and Summary of Evidence

The interventions and evidence summaries presented in the four separate tables above in Section *VII.a-c* where all conducted with the same search strategy; however, each table yielded different results (selection criteria and the search strategy results). These differences are identified below is the table titled *Differences in the Selection Criteria and Search Results for each Clinical Question*. Additionally, the corresponding references for each clinical question are presented.

9.1 Inclusion Criteria

The aim of this evidence summary is to gather information from a systematic review about the benefits and risk of a drug in a specific health problem. For this reason we include in the summary the results from a rigorous systematic review, prioritizing Cochrane reviews. When a Cochrane review is not available or it is not suitable to respond the scope of the clinical question, we consider the inclusion of a systematic review that at least: i) includes a clearly defined inclusion criteria; ii) reports a recent search in at least two databases; and iii) reports any efforts from authors to assess the risk of bias from the included studies.

These criteria are the minimum requirements established by the Centre for Reviews and Dissemination to include a systematic review in the Database of Abstracts of Reviews of Effects (DARE; www.crd.york.ac.uk/crdweb/AboutPage.asp). For the specific purposes of the "Cost studies" section we include the results from an economic evaluation, that is; a comparison of two or more interventions or care alternatives (including cost-benefit analyses, cost-utility analyses, and cost-effectiveness analyses).

9.2 Search for Studies

The inclusion criteria described above determines the search for the studies planned. We design specific search algorithms to search the AHRQ Effective Health Care Program and The Cochrane Library as the main source to retrieve high quality systematic reviews. Each search in these two resources is complemented with a search in MEDLINE (accessed through PubMed) with the purpose of check any additional or more recent systematic review. The search is performed without any limitation, with the exception of PubMed in which we limit the search to the validated subset of systematic reviews (systematic[sb]). As we included only economic evaluations in the "Cost studies" section we limit the search to the NHS EED Database. In those cases that the NHS EED Database does not provide relevant results, we perform a specific search in MEDLINE, limiting the search algorithm designed to retrieve systematic review with the term cost*[tiab]. The search to develop the present clinical question was performed in May 2013, with the search strategies detailed below (Section 9.4).

9.3 Rating the Quality of the Evidence

Each evidence summary provides a rating of the quality of evidence following the GRADE guidance. GRADE specifies four categories (high, moderate, low, and very low) that are applied to the body of evidence that supports each assessed outcome. In the context of a synthesis of the evidence the quality of evidence reflects the confidence that the estimates of the effect are correct. For each clinical question one experienced researcher collects in a table the number of studies and patients included in these studies that set the body of evidence for each specific outcome discussed in the "Benefits" and "Risks" sections. The quality of evidence is then rated for each specific outcome and a final category is provided, commenting the main limitations that compromise the quality of evidence. All the information collected in the table, and the details required to the rating of the quality of evidence are obtained from the assessed systematic review used to develop the evidence summary.

9.4 Selection Criteria

One experienced researcher screens the results from the search applying the inclusion criteria commented above. If a Cochrane review is identified, it is selected to develop the evidence summary. When a Cochrane review is not suitable to respond to the scope of the formulated clinical question, the references from MEDLINE are screened.

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
What is the efficacy and safety of tacrolimus compared to cyclosporine in the treatment of adult kidney transplant?	For the purposes of this clinical question, a Cochrane review was identified from the records retrieved from the Cochrane Database of Systematic Reviews (*3*).	**Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ transplantation 24 hits immunosuppress* 8 hits **Cochrane Database of Systematic Reviews: (The Cochrane Library; Issue 4 of 12, April 2013)** transplantat* AND immunosuppress* 365 hits **MEDLINE (accessed via PubMed)** tacrolimus[ti] AND cyclosporine*[ti] AND systematic[sb] 13 hits tacrolimus[tiab] AND cyclosporine[tiab] AND renal[ti] AND systematic[sb] 8 hits tacrolimus[tiab] AND cyclosporine[tiab] AND kidney[ti] AND systematic[sb] 10 hits **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (Tacrolimus):TI AND (Cyclosporine):TI AND (kidney OR renal):TI IN NHSEED 4 hits
What is the efficacy and safety of tacrolimus compared to cyclosporine in the treatment of adult liver transplant?	For the purposes of this clinical question, a Cochrane review was identified from the records retrieved from the Cochrane Database of Systematic Reviews (*3*).	**Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ transplantation 24 hits immunosuppress* 8 hits **Cochrane Database of Systematic Reviews: (The Cochrane Library; Issue 4 of 12, April 2013)** transplantat* AND immunosuppress* 365 hits **MEDLINE (accessed via PubMed)** tacrolimus[ti] AND cyclosporine*[ti] AND systematic[sb] 13 hits **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (Tacrolimus):TI AND (Cyclosporine):TI AND (liver OR hepatic):TI IN NHSEED 1 hits

Differences in the Selection Criteria and Search Results for each Clinical Question		
Question	**Selection criteria**	**Search strategy results**
What is the efficacy and safety of tacrolimus compared to cyclosporine in the treatment of adult heart transplant?	For the purposes of this clinical question, no Cochrane reviews were available and from the 13 references obtained in MEDLINE only the assessed systematic review (8) fulfilled with the inclusion criteria mentioned above.	**Agency for Healthcare Research and Quality – Effective Health Care Program** http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ transplantation 24 hits immunosuppress* 8 hits **Cochrane Database of Systematic Reviews: (The Cochrane Library; Issue 4 of 12, April 2013)** transplantat* AND immunosuppress* 365 hits tacrolimus AND cyclosporin* 836 hits **MEDLINE (accessed via PubMed)** tacrolimus[ti] AND cyclosporine*[ti] AND systematic[sb] 13 hits cost*[tiab] AND tacrolimus[ti] AND cyclosporine[ti] AND (cardiac[ti] OR heart[ti]) 0 hits **NHS EED (accessed via Centre for Reviews and Dissemination databases)** (Tacrolimus) AND (Cyclosporine) AND (cardiac OR heart) IN NHSEED 0 hits
What is the efficacy and safety of tacrolimus compared to cyclosporine in the treatment of adult bone marrow and stem cell transplant?	For the purposes of this clinical question, no Cochrane reviews were available. A specific search for clinical trials in the Cochrane Central Register of Controlled Trials and MEDLINE retrieved 27 references. We excluded 19 of these by reading their title and abstract. From 8 full text studies assessed in detail we excluded two studies that included a comparison with methotrexate (*14,15*), a narrative review (*4*), an open label study (*16*), and a scientific communication with the results of one of the included trials in this clinical question (*11,17*).	**Cochrane Central Register of Controlled Trials (The Cochrane Library; Issue 5 of 12, May 2013)** #1 tacrolimus:ti,ab,kw 1 898 hits #2 cyclosporine:ti,ab,kw 3793 hits #3#1 and #2 774 hits #4 marrow:ti,ab 4328 hits #5stem cell:ti,ab 3237 hits #6 #4 or #5 6665 hits #7 #3 and #6 16 (15 in clinical trials) hits **MEDLINE (accessed via PubMed)** #1 tacrolimus[tiab] 10257 hits #2 cyclosporine[tiab] 24654 hits #3 #1 AND #2 2904 hits #4 marrow[tiab] 171543 hits #5 stem cell[tiab] 78660 hits #6 #4 OR #5 233141 hits #7 #3 AND #6 159 hits #8 randomized controlled trial [pt] 344799 hits #9 controlled clinical trial [pt] 85645 hits #10 randomized [tiab] 289413 hits #11 placebo [tiab] 149216 hits #12 clinical trials as topic [mesh: noexp] 163378 hits #13 randomly [tiab] 197503 hits #14 trial [ti] 115350 hits #15 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 849435 hits #16 animals [mh] NOT humans [mh] 3786976 hits #17 #15 NOT #16 785182 hits #18 #7 AND #17 22 hits

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10. Additional References

The following references are those cited in Section 2 (Public Health Relevance), Section 4 (Medicine Characteristics and Pharmacological Information) and Section 8 (Special Considerations and Additional Comments). References supporting the intervention and summary of evidence are available in Sections 9.5 - 9.8.

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Annex 8

Review of the Available Evidence of Trastuzumab 150mg Powder for Injection for Potential Inclusion in the Pan American Health Organization Strategic Fund Medicine List

Annex 8: Table of Contents

1. Introduction to the PAHO Strategic Fund

The PAHO Regional Revolving Fund for Strategic Public Health Supplies (Strategic Fund) was created by the Director of the Pan American Health Organization (PAHO) at the request of Member States of the Organization, in September 1998 during the 35th session of the Pan American Sanitary Conference.

The Strategic Fund is a regional mechanism which aims to strengthen the supply and management of essential public health supplies in Member States by providing technical cooperation and procuring quality, safe and effective supplies at affordable prices obtained by leveraging the advantages of economies of scale.

To accomplish this objective the Strategic Fund publishes a list of medicines available for procurement in name of the Organization's Member States. The list utilizes as a foundation the World Health Organization (WHO) Essential Medicines List (EML); however, recently there has been a significant increase in Member State requests to procure products not included in the WHO EML.

In order to meet the needs of PAHO Member States the PAHO Director has created an external Expert Committee to review requests for inclusion of medicines not included in the WHO EML. This Expert Committee will allow PAHO to implement a decision making mechanism in agreement with concepts of quality, efficacy, safety and when available, information related to the value they provide in relation to their cost.

The committee will work exclusively on requests to update the SF medicine list, which will enable PAHO to adequately respond to the needs of PAHO Member States. Due to this specific function and objective, this committee does not seek to replace or complement the work performed by WHO in developing the EML or by Member State pharmacotherapeutic committees who decide to include or exclude medicines from national essential medicine lists (formularies). As a result, the recommendations issued by this EC should not be utilized as references for the development of other essential medicine lists or treatment guidelines.

2. Public Health Relevance (*1-3*)

2.1 NCDs in the Region of the Americas

Over the last decades, noncommunicable diseases (NCDs) have become the leading cause of morbidity and mortality across the globe while imposing a growing threat to international development goals and economic growth as well as contributing to dramatic rises in health care expenditures.

The main NCDs principally include cardiovascular disease, cancer, diabetes and respiratory diseases and are accompanied by various common risk factors rising at a rapid pace. In the Americas region, NCDs are responsible for 3 out of every 4 deaths with cardiovascular diseases and cancer as the leading causes responsible respectively for 1.9 million and 1.2 million deaths each year. More than one third of these deaths are premature and occur in people under the age of 70 years old therefore leading to serious repercussions on social and economic development.

Noncommunicable diseases not only slow down development but also place a heavy financial burden on patients, healthcare and governments. The costs to overall health systems are expect to rise as governments are expected to increase funding to prevent and treat these diseases. Confronting the rising costs constitutes a real challenge in low and middle income countries of the Americas where economic growth is often compromised and healthcare systems have to manage access and equity issues. Patients are facing similar issues, as in many countries healthcare costs are paid out-of-pocket and the impact of NCDs on household budgets and healthcare expenditures can often lead to catastrophic spending and impoverishment.

In some countries of the region, out-of-pocket expenditures account for 78% of spending on medicines. Cardiovascular diseases constitute an important family expenditure on healthcare and can become an enormous economic and social burden in low-and-middle income countries. For example, patients suffering from more than two chronic diseases and taking more than two medicines for these conditions account for 10% of all patients in some countries. Health expenditures for this population can reach 50% of the overall health expenditure. Hence, in Latin America, out-of-pocket expenses related to NCDs and health expenditures accounting for chronic diseases represent a critical health care and financial issue.

In response to the NCD situation in the Americas, the 28th Pan American Sanitary Conference in September 2012, adopted the Regional Strategy for the Prevention and Control of Noncommunicable Diseases (Resolution CSP28.R13 aims to:

> "reorient and strengthen health systems to improve coverage, access to and quality of care provided to the people with NCDs or their risk factors, based on primary health care"

This process is linked with the WHO voluntary global NCD targets for 2025, which aims to achieve the following:

- 25% relative reduction of premature mortality due to noncommunicable diseases
- 80% coverage of essential NCD medicines and technologies
- 50% coverage of drug therapy and counseling.

As a critical component of PAHO's response to these issues, the Strategic Fund is increasing support and assistance to Member States by amplifying the list of NCD medicines for countries to procure. Thus, increasing access to quality drugs and helping ease the increasing financial burden, specifically for new or high cost medicines.

The Strategic Fund has initiated a process to review the available evidence regarding the efficacy, safety and cost-effectiveness of NCD medicines, particularly for cardiovascular diseases and cancer. The following document presents the status of the medicine, basic pharmacological information, the evidence comparing the requested medicine and its alternative for the specified indications and other relevant information.

2.2 Cancer Health Situation in the Americas

In the Region of the Americas, cancer, the second leading NCD, represents a major health and economic concern, particularly due to the increasing incidence and the high costs of treatment. In Latin America, an estimated 114,900 women are diagnosed with breast cancer every year and there are approximately 37,000 deaths yearly caused by the disease. Breast cancer is considered the most common cancer among women and having the highest death rates in Latin America.

The high incidence and mortality rates due to the disease represent a high economic and social burden in countries like Argentina or Uruguay, whose rates are similar to Europe and the USA. Although other countries in the region have lower rates and there is a lot of variability in the Region, countries like Mexico and Brazil are expected to reach a similar demographic structure as Argentina by 2020.

The curing rate for these diseases is generally very high when detected at an early stage and treated accordingly. However, the Region is still struggling with late stage diagnosis and limited access to early detection and treatment measures. Universal health-coverage is still lacking in many countries and allocating the necessary resources for effective diagnosis and treatment of the disease constitutes a real problem for many of PAHO's Member States.

Implementing evidence-based strategies for cancer prevention, early detection and management of therapy for patients already diagnosed would enable to reduce the burden imposed by this non communicable disease. The access to cancer treatments can often represent the last alternative to increase life span and the quality of life of patients living with cancer and can make a tremendous difference in the overall survival of HER2+ breast cancer women population.

3. Entity Supporting the Application and Requested Indications

3.1 Entity Supporting Application

The PAHO Noncommunicable Disease Unit (NMH/ND) is requesting and supporting this application.

3.2 Requested Indications

Trastuzumab, a monoclonal antibody, has been requested for the treatment of adult women with HER2+ early stage or HER2+ advanced metastatic stage breast cancer. In January 2013, a proposal to include trastuzumab for the treatment of adult women with HER2+ early stage breast cancer in the WHO Essential Medicine List (EML) was submitted to the WHO Selection Committee, which has not yet issued an official decision for trastuzumab.

As the evidence for the early breast indication has been compiled by WHO, this document focuses on the HER2+ advanced metastatic breast cancer indication. For further information concerning the early breast cancer indication, please refer to the 19th Expert Committee on the Selection and Use of Essential Medicine section in the WHO website.

- Application:

  http://www.who.int/selection_medicines/committees/expert/19/applications/trastuzumab/en/index.html .

- Expert Reviews:

  http://www.who.int/selection_medicines/committees/expert/19/reviews/en/index.html

4. Medicine Characteristics and Pharmacological Information (*4-11*)

4.1 General Information

1) Medicine name (INN)	Trastuzumab
2) ATC (anatomical therapeutic chemical- WHO Drug classification system)	L01XC03
3) Reference trade name: (1. Innovator & 2. Generic - when available some examples provided)	1. Innovator: Herceptin (Genentech, USA, Hoffmann La Roche, Worldwide) 2. Generic: No generic available
Therapeutic class (according to classification in the WHO EML)	Monoclonal antibody/HER2-blocker (not on WHO EML list)

4.2 Mechanism of Action

Trastuzumab, a recombinant DNA-derived humanized monoclonal antibody, inhibits the proliferation of tumor cells overexpressing HER2 receptors by selectively targeting the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2).

4.3 Pharmacokinetic/Pharmacodynamics Considerations

The pharmacokinetics of trastuzumab have been studied in women with metastatic breast cancer.

- Absorption: Cmax=377mcg/mL (500mg); 123mcg/mL (4mg/kg initial, then 2mg/kg weekly);216mcg/mL (8mg/kg initial, then 6mg/kg every 3 weeks).
- Distribution: Vd=44mL/kg.
- Metabolism: unknown, CYP450: unknown
- Excretion: T1/2=2 days (10mg), 12 days (500mg), 6 days (4mg/kg initial, then 2mg/kg weekly), 16 days (8mg/kg initial, then 6mg/kg every 3 weeks)

4.4 Dosage, Preparation and Administration

In the US, trastuzumab is supplied as a lyophilized, sterile powder containing 440 mg trastuzumab per vial under vacuum. Each carton contains one vial of 440 mg trastuzumab and one 20 mL vial of BWFI (Bacteriostatic Water for injection) containing 1.1% benzyl alcohol.

The reconstituted solution of trastuzumab is a solution yielding to a concentration of 21mg/ml, irrespective of the format 440mg or 150mg vial.

- *Recommended dose and dose adjustments:*

  1. Early breast cancer (EBC), adjuvant treatment:
     - Treatment duration:
       1 year or until disease reoccurs or until treatment is discontinued because of cardiac toxicity
     - Administration: One dose every 3 weeks or once per week
       One dose every 3 weeks:
       - » initial loading dose 8mg /kg administered as a 90-minute infusion
       - » maintenance dose: 6mg/kg repeated every 3 weeks as a 30 to 90-minute infusion (if loading dose well tolerated, can reduce time of infusion to 30 minutes starting second dose);

       One dose every week:
       - » Initial loading dose: 4mg/kg administered as a 90-minute infusion
       - » Maintenance dose: 2mg/kg every week as a 30-minute infusion
  2. Metastatic breast cancer (MBC) treatment
     - Treatment duration:
       Until progression of disease
     - Administration: Weekly
       - » Initial loading dose: 4mg/kg administered as a 90-minute infusion
       - » Maintenance dose: 2mg/kg every week as a 30-minute infusion
- *Preparation for administration:* Please see monograph for detailed procedure (*7-10*)

- *Administration:*

  1. Do not administer trastuzumab as an intravenous push or bolus.
  2. Do not mix or dilute with other drugs or with dextrose solution for infusion.
  3. Trastuzumab should be administered by a qualified health care professional.
  4. Weekly or 3-weekly schedule
     - Loading dose should be administered by intravenous (IV) infusion over 90 minutes. Patients should be observed for chills and fever or other infusion reactions (see side effects). If good tolerance, the maintenance doses can be administered over 30 minutes.

4.5 Contraindications

Trastuzumab is contraindicated if hypersensitivity to trastuzumab, Chinese Hamster Ovary (CHO) cell proteins, or any component of this product.

4.6 Warnings/Precautions

- *Cardiotoxicity*

  Trastuzumab can result in congestive heart failure and left ventricular dysfunction. The incidence increases when trastuzumab is administered concomitantly with other cardiac toxic drugs (anthracyclines, taxanes, carboplatin, cyclophosphamide, etc.). Assess left ventricular function prior and during treatment and up to 2 years following completion of therapy.

- *Infusion reaction- pulmonary toxicity*

  Higher incidence in the first 24 hours. Withhold treatment if dyspnea or significant hypotension until symptoms resolve. Discontinue permanently if severe reactions such as angioedema, anaphylaxis, acute respiratory distress, interstitial pneumonitis. Pulmonary toxicity also includes non-cardiogenic pulmonary edema, pulmonary fibrosis, pulmonary infiltrates, pleural effusions and pulmonary insufficiency and can arise following infusion reactions.

- *Embryo-fetal toxicity*

  Avoid use of trastuzumab in pregnant women. It can result in impairment of fetal renal growth or impairment of renal function resulting in oligohydramnios manifestations (pulmonary hypoplasia, skeletal abnormalities and neonatal death). Counsel women on potential hazards to the fetus from Herceptin exposure during pregnancy and provide contraception counseling to women of childbearing potential.

- *Caution with adjuvant myelosuppressive chemotherapy*

  Increases the incidences of NCI CTC Grade 3-4 neutropenia and of febrile neutropenia.

4.7 Use in Specific Populations

- *Pregnancy:* Category D Trastuzumab can cause fetal harm if administered during pregnancy (see Warnings). Avoid during pregnancy and counsel childbearing women on proper contraception therapy.

- *Nursing mothers:* It remains unknown as to whether trastuzumab is excreted in human milk. Considering the potential excretion in breast milk, it has to be determined whether to discontinue nursing, or discontinue drug, taking into account the half-life of trastuzumab and the importance of the medicine to the mother.

- *Pediatric use:* Trastuzumab's safety and effectiveness have not been established in pediatric patients.
- *Geriatric use:* No consensus reached according to the effectiveness and safety of trastuzumab in the elderly. Some studies have noted no difference as others noted an increase in the risk of cardiac dysfunction in geriatric patients.

4.8 Side Effects

The list of adverse events is compiled using data from clinical trials and post marketing experience. Note that trastuzumab is often used in combination with other chemotherapy medicines in clinical trials and is compared to these agents as a reference for adverse events. The percentage of adverse events varies according to the clinical trials indications.

Here is a list of some of the most common and some of the most serious and rare adverse events listed in monographs from clinical trials. For the exhaustive list, please refer to NRAs trastuzumab's monographs.

Very Common (>1/10):		Serious and/or Rare:
Blood and lymphatic system disorders	■ Febrile Neutropenia	■ Cardiomyopathy, congestive heart failure and decrease in LVEF ■ Infusion reactions (most common are fever and chills but more serious and rare include hypersensitivity, anaphylaxis and angioedema) ■ Anemia requiring transfusion ■ Febrile neutropenia ■ Pulmonary toxicity (pneumonitis, pulmonary infiltrates, interstitial pneumonitis, etc.) ■ Thrombosis/embolism ■ Renal toxicity (severe renal failure, membranous glomerulonephritis, fibrillary glomerulonephritis)
Nervous system disorders	■ Headache ■ Dizziness ■ Tremor	
Eye disorders	■ Conjunctivitis ■ Increased lacrimation	
Cardiac disorders	■ Blood pressure decreased or increased ■ Heart beat irregular ■ Palpitation ■ Cardiac flutter ■ Ejection fraction decreased	
Vascular disorders	■ Hot flush	
Respiratory, thoracic and mediastinal disorders	■ Wheezing ■ Dyspnea ■ Cough ■ Epistaxis ■ Rhinorrhea	
Gastrointestinal disorders	■ Diarrhea ■ Vomiting ■ Nausea ■ Lip swelling ■ Abdominal pain	
Skin and subcutaneous disorders	■ Erythema ■ Rash ■ Swelling face	
General disorders and administration site conditions	■ Asthenia ■ Chest pain ■ Chills ■ Fatigue ■ Influenza-like symptoms ■ Infusion related reaction ■ Pain ■ Pyrexia	

4.9 Main Interactions

According to the information provided in the monographs, no drug interaction studies were performed with trastuzumab in humans. There is no strong evidence supporting clinically significant interactions with the concomitant medications used in clinical studies. However, clinical studies have indicated that the pharmacokinetics of trastuzumab and antineoplastic agents may influence each other as follows:

- *Effect of trastuzumab on the pharmacokinetics (PK) of other antineoplastic agents*

  Pharmacokinetic data from various studies derived from combinations between trastuzumab and antineoplastic agents such as paclitaxel, docetaxel, doxorubicin or cisplatin overall concluded that the PK of these agents is not affected by the concurrent use of trastuzumab. The exposure to bioactive metabolites, the slight increase in concentration or the minor prolongation of half-life of antineoplastic agents was not significant enough to critically influence PK.

- *Effect of antineoplastic agents on trastuzumab pharmacokinetics (PK)*

  In clinical studies, no clear evidence of variation in the pharmacokinetic effect of trastuzumab was found when it was administered concomitantly with other antineoplastic agents (paclitaxel, docetaxel).

4.10 Other

- *Storage and stability:*

  Vials of Herceptin (trastuzumab) are stable at 2-8°C (36–46°F) prior to reconstitution. Reconstituted Herceptin should be stored 2-8°C and discarded after 28 days. It SWFI without preservative is used to reconstitute Herceptin, it should be immediately used and any unused portion should be discarded. Do not freeze reconstituted solution. The diluted infusion solution should be used immediately and the product is not intended to be stored after dilution unless diluted under controlled and validated aseptic conditions. However, solutions for infusion diluted with 0.9% NaCl USP have been shown stable up to 24 hours at 30°C but the lack of effective preservative suggests it should be kept refrigerated under 2-8°C for a maximum of 24h, if ever stored and not used immediately.

- *Special handling:*

  Biologic agent should be handled and disposed of using biohazard precautions. Unused or empty vials should be returned to the pharmacy for proper disposal.

- *Toxicology (reproductive toxicology studies and impairment of fertility):*

  Animal studies have been conducted with female monkeys and revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels. No male fertility studies have been conducted so far.

- *HER2 testing and selection of patients/diagnostics tests:*

  Considering that the patients involved in clinical trials all expressed HER2 receptors, it is necessary to perform detection of HER2 protein overexpression and HER2 gene amplification for selection of patients to receive Herceptin therapy as this population is the only one that has been studied and in which Herceptin's efficacy and safety has been shown. Approved tests should be used and should be performed in laboratories that demonstrated proficiency in this specific technology.

- *Therapy monitoring (monitoring facilities and skills):*

  Cardiac monitoring: In order to reduce the risk of serious cardiac adverse events, it is imperative to conduct a cardiac assessment (history, physical examination, determination of left ventricular

ejection fraction (LVEF) by echocardiogram or MUGA scan) and monitor cardiac function according to the following schedule (based on monograph):

1. Baseline LVEF measurement prior to initiation of trastuzumab
2. LVEF measurements every 3 months until completion of trastuzumab
3. Repeat LVEF measurement at 4 week intervals if trastuzumab is withheld for significant left ventricular cardiac dysfunction
4. LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy.

5. Alternatives to Trastuzumab Available in the Strategic Fund

The current version of the Strategic Fund medicine list includes cytotoxic agents and adjuvant medicines (e.g. carboplatin, cyclophosphamide, paclitaxel); however, the list does not contain any monoclonal antibodies for the treatment of breast cancer.

The following document provides the supporting evidence regarding the efficacy and safety of trastuzumab used as a single agent or in combination therapy when treating women with HER-2 positive advanced or metastatic breast cancer.

6. Guidelines Including the Use of the Medicine in Relation with the Proposed Indications

Below are presented some of the available guidelines for the treatment and management of breast cancer.

- National Comprehensive Cancer Network (NCCN): Guideline Breast Cancer 2013http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
- National institute for Health and Care Excellence (NICE): Early and locally advanced breast cancer: diagnosis and treatment Feb. 2009 reviewed March 2012 http://www.nice.org.uk/CG80
- Breast Health Global Initiative (BHGI): Guidelines for International Breast Health and Cancer Control-implementation 2008 http://portal.bhgi.org

7. Intervention and Summary of Evidence

The indications specified in the clinical questions presented below are based on input from the PAHO technical unit supporting this request (NMH/ND) and three Member States. The evidence presented in this section was obtained in collaboration with the Asociación Colaboración Cochrane Iberoamericana – Centro Cochrane Iberoamericano (ACCIb-CCIb).

For trastuzumab, the intervention and summary evidence has been compiled in one table, with the corresponding tables.

The search strategy and references supporting the intervention and summary of evidence are available in *Section 9* of this dossier.

7.1 Trastuzumab in Women with Her-2 Positive Advanced Breast Cancer

CLINICAL QUESTIONS
What is the efficacy and safety of trastuzumab used as a single agent or in combination therapy when treating women with HER-2 positive advanced or metastatic breast cancer?

CONTEXT	Trastuzumab in HER-2 positive advanced breast cancer
Breast cancer is the most common type of cancer among women that have one in nine lifetime risk of developing it. Metastatic breast cancer is an advanced stage of the disease that appears when it has spread to other organs. An estimated 5% of women are newly diagnosed with metastatic breast cancer, and approximately 30% of women that has been diagnosed with localized breast cancer will later develop metastatic breast cancer. Metastatic breast cancer tumours that over express the HER2 protein (HER2+) grow and divide more quickly. Women with HER2+ tumours generally have a worse prognosis than women with HER2- tumours. Approximately 20 to 30% of women with metastatic breast cancer have HER2+ tumours, of which about 50% will also be hormone receptor positive. The goal of treatment in metastatic breast cancer is to palliate symptoms, prolong survival and maintain a good quality of life with minimal adverse events. Choice of treatment depends on previous therapy, hormone receptor status, HER2 status and the extent of the disease. Some studies have discussed the potential of trastuzumab, alone or combined with other chemotherapy in the treatment of patients with metastatic breast cancer who have HER2+ tumours.	

INTERVENTION	Trastuzumab in HER-2 positive advanced breast cancer
Trastuzumab combined with chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) versus chemotherapy alone for the first line of metastatic disease The addition of trastuzumab to chemotherapy is more effective than chemotherapy alone in improving overall and progression-free survival, tumor response and the duration of the response. *Moderate quality evidence.* The addition of trastuzumab to chemotherapy compared to chemotherapy alone has a higher risk of cardiac dysfunction of New York Heart Association class III or IV. *Moderate quality evidence.*	
Trastuzumab plus anastrozole versus anastrozole alone in hormone receptor-positive metastatic breast cancer Trastuzumab plus anastrozole is superior to anastrozole alone in improving progression-free survival. *Moderate quality evidence*. Trastuzumab plus anastrozole compared to anastrozole alone does not differ in improving overall survival. *Moderate quality evidence*. Trastuzumab plus anastrozole compared to anastrozole alone has a higher risk of grade 3 and 4 adverse events. *Moderate quality evidence*.	

Summary of evidence	
Benefits	NICE conducted a systematic review (*1*) to develop its technology appraisal guidance 34 on trastuzumab for metastatic breast cancer (MBC) with tumors expressing human epidermal growth factor receptor 2 (HER2+) (*2*). The review included one RCT that compared trastuzumab plus chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) versus chemotherapy alone in the first line of metastatic disease. The study included women with HER2-overexpressing MBC at level 2+ or 3+ who had not received prior treatment for metastatic breast cancer (n=469) (*3*). Patients had not previously received anthracyclines in the adjuvant setting. Trastuzumab was administered in weekly infusions as long as the treatment was considered to be beneficial. The results of the systematic review led NICE to recommend trastuzumab in combination with paclitaxel in those women with MBC HER2+ who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate (*2*). The systematic review also had the objective to assess trastuzumab used as a single agent in the second line therapy for MBC in HER2+ women, but did not found RCT on that topic and based their assessment on two case series studies and one trial comparing different doses of trastuzumab. Another systematic review (*4*) developed for a NICE technology appraisal guidance (*5*) focused in the effects of trastuzumab in combination with an aromatase inhibitor for first-line treatment in postmenopausal women with metastatic hormone receptor-positive HER2+ breast cancer. This review included only one RCT (*6*) that compared trastuzumab plus anastrozole with anastrozole alone in postmenopausal women with hormone-receptor-positive and HER2+ metastatic breast cancer. The TAnDEM trial included 207 postmenopausal women with hormone-receptor-positive and HER2+ metastatic breast cancer with an ECOG performance status of 0 or 1. The median age of patients was 56 years in the trastuzumab plus anastrozole group and 54 years in the anastrozole alone group. The median number of metastatic sites was two and 56% of patients had bone metastases. The primary outcome was progression-free survival. The secondary outcomes included overall survival, time to progression and overall response rate. An additional RCT (*7*) aimed to compare trastuzumab plus letrozole with letrozole alone but the study was stopped early because of slow recruitment. The results of the review resulted in a recommendation against trastuzumab in combination with an aromatase inhibitor for first-line treatment in postmenopausal women with metastatic hormone receptor-positive breast cancer that overexpresses HER2 (*5*). **Benefits of trastuzumab combined with chemotherapy versus chemotherapy alone for the first line of metastatic disease** The addition of trastuzumab to chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) compared to chemotherapy alone was associated with: i) a longer time to disease progression (median of 7.4 vs. 4.6 months; P<0.001); ii) a higher rate of objective response (50% vs. 32%, P<0.001); iii) a longer duration of response (median of 9.1 vs. 6.1 months; P<0.001); iv) a lower rate of death at 1 year (22% vs. 33% percent, P=0.008); v) longer survival (median survival of 25.1 vs. 20.3 months; P=0.01); vi) and a 20% reduction in the risk of death. **Trastuzumab plus anastrozole versus anastrozole alone in hormone receptor-positive metastatic breast cancer** The median progression-free survival in the TAnDEM trial was 5.8 months (95% CI 4.6 to 8.3) for the trastuzumab plus anastrozole group and 2.9 months (95% CI 2.1 to 4.5) for the anastrozole alone group (HR for progression 0.55, 95% CI 0.41 to 0.74, p<0.001). The median overall survival was 34.1 months (95% CI 23.9 to 52.0) for the trastuzumab plus anastrozole group and 28.6 months (95% CI 17.4 to 40.0) for the anastrozole alone group (HR for death 0.85; 95%CI not reported, p=0.45).

Summary of evidence	
Risks	Benefits of trastuzumab combined with chemotherapy versus chemotherapy alone for the first line of metastatic disease One RCT found that the addition of trastuzumab to an anthracycline in combination with cyclophosphamide was associated with higher risk of adverse events compared with chemotherapy alone (*3*). The most important adverse event was cardiac dysfunction of New York Heart Association class III or IV, which occurred in 27 percent of the group given an anthracycline, cyclophosphamide, and trastuzumab; 8 percent of the group given an anthracycline and cyclophosphamide alone; 13 percent of the group given paclitaxel and trastuzumab; and 1 percent of the group given paclitaxel alone. Although the cardiotoxicity was potentially severe and, in some cases, life-threatening, the symptoms generally improved with standard medical management. Trastuzumab plus anastrozole versus anastrozole alone in hormone receptor-positive metastatic breast cancer One RCT (*6*) found that patients who received trastuzumab plus anastrozole were more likely to experience adverse events compared with patients who received anastrozole alone (87% compared with 65%). Incidence of grade 3 and 4 adverse events was 23% and 5%, respectively, in the trastuzumab plus anastrozole arm, and 15% and 1%, respectively, in the anastrozole alone arm. In this trial one woman in the combination arm experienced New York Heart Association class II congestive heart failure. Fatigue, diarrhea and vomiting were among the most common adverse events (21%, 20% and 21% respectively in the trastuzumab plus anastrozole group compared with 10%, 8% and 5% in the anastrozole alone group).
Comments/ Applicability	Benefits of trastuzumab combined with chemotherapy versus chemotherapy alone for the first line of metastatic disease Trastuzumab when used in combination with chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) seems to be more effective than chemotherapy alone for the treatment of metastatic breast cancer overexpressing HER2 at level 3+ in women who have not received prior treatment for metastatic breast cancer. The evidence included in the review assessed (*1*) comes from a period in which many patients who developed metastatic breast cancer had not been treated with chemotherapy. However nowadays patients with HER2+ breast cancer are usually treated with other chemotherapy drugs before developing metastases.
	Trastuzumab plus anastrozole versus anastrozole alone in hormone receptor-positive metastatic breast cancer An issue that needs to be considered relates to the generalizability of the results of these trials to the population of interest in the present days. None of the patients in the TAnDEM trial have received prior treatment with trastuzumab, an issue that is not surprising as, at the time the trial was recruiting, the use of trastuzumab for patients with early or advanced breast cancer was relatively rare. This can contrasts very much, however, with what happens in clinical practice today. Now, when a patient is diagnosed with early HER2+ breast cancer, trastuzumab is the standard treatment of choice. In consequence, only de novo patients with HR+/HER2+ MBC (i.e. trastuzumab-naïve patients) will be eligible for trastuzumab and anastrozole (*5*).

Summary of evidence	
Cost studies	Published economic evaluations of trastuzumab for the treatment of HER2+ metastatic breast cancer have arrived at different conclusions regarding the cost-effectiveness of this drug, despite comparative efficacy being demonstrated by a small set of randomised controlled trials. A systematic literature review of economic evaluations in this setting (*8*) identified fifteen studies that compared the incremental costs and outcomes of trastuzumab versus a comparator. In the evaluations that estimated efficacy using an RCT, the key drivers of the conclusions regarding cost-effectiveness were: i) the approach used to estimate overall survival in the control group given crossover to trastuzumab following progression in the trials; ii) the inclusion of treatment beyond progression; iii) inclusion of wastage due to unused vial portions, iv) adverse events; v) and the cost of HER2 testing. Four of the included evaluations used non-randomised approaches to estimate efficacy, thus introducing the potential for confounding. As a result these evaluations reported relatively optimistic estimates of comparative effectiveness. Finally the evaluations used different thresholds to determine whether treatment with trastuzumab was cost-effective. The economic evaluations with the more feasible results were those that derived in the NICE technology appraisals commented above (*2,5*). The NICE technology appraisal guidance 34 concluded that trastuzumab combination therapy was likely to be lower than £37,500 per QALY gained (*2*). In the other hand, the NICE technology appraisal guidance 257 concluded that the most plausible ICER for trastuzumab plus an aromatase inhibitor would be at least £51,000 per QALY gained (*5*).

Table 1. Characteristics of the RCT Included into the Considered Systematic Reviews (*1,4*)

Study ID	Design (Sample size)	Patients	Intervention	Outcomes
Slamon 2001 (3)	RCT (n=469)	Women with metastatic breast cancer that overexpressed HER2	Patients who had not previously received adjuvant (postoperative) therapy with an anthracycline were treated with doxorubicin or epirubicin and cyclophosphamide alone or with trastuzumab. Patients who had previously received adjuvant anthracycline were treated with paclitaxel alone or paclitaxel with trastuzumab. Trastuzumab (4 mg/kg by intravenous infusion on day 1, followed by 2 mg/kg weekly) until there was evidence of disease progression.	**Primary:** Time to disease progression. **Secondary:** Rate of objective response, the duration of a response, the time to treatment failure and survival.
Kaufmfman 2009 (6) TAnDEM trial NCT00022672	RCT (n=207)	Postmenopausal women with HER2/hormone receptor-copositive metastatic breast cancer	Anastrozole 1 mg/d orally (control) or trastuzumab (4 mg/kg by intravenous infusion on day 1, followed by 2 mg/kg weekly) plus anastrozole (1 mg/d orally)	**Primary:** Progression-free survival **Secondary:** Clinical benefit rate, overall response rate, time to progression, duration of response, time to response, overall survival, and 2-year survival rates.

Table 2. GRADE Evaluation Of Clinical Outcomes: (Trastuzumab Combined with Chemotherapy Versus Chemotherapy Alone for the First Line of Metastatic Disease (Assessment for all the Outcomes from Data in Reference *1*)

Number of studies (N))	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
1 (469)	Time to disease progression	trastuzumab combined with chemotherapy chemotherapy alone	4	0	0	-1	0	Moderate	Results are applicable only to trastuzumab-naïve patients
1 (469)	Overall survival	trastuzumab combined with chemotherapy chemotherapy alone	4	0	0	-1	0	Moderate	Results are applicable only to trastuzumab-naïve patients
1 (469)	Rate of objective response	trastuzumab combined with chemotherapy chemotherapy alone	4	0	0	-1	0	Moderate	Results are applicable only to trastuzumab-naïve patients
Trastuzumab plus anastrozole versus anastrozole alone in hormone receptor-positive metastatic breast cancer (assessment for all the outcomes from data in reference 4)									
1 (207)	Time to disease progression	trastuzumab combined with anastrozole anastrozole alone	4	0	0	-1	0	Moderate	Results are applicable only to trastuzumab-naïve patients
1 (207)	Overall survival	trastuzumab combined with anastrozole anastrozole alone	4	0	0	-1	0	Moderate	Results are applicable only to trastuzumab-naïve patients
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									

8. Special Considerations and Additional Comments (*12-20*)

8.1 Regulatory Status of the Product in National Regulatory Authorities (NRAs)

The following table reflects the regulatory status of the product (innovator and generic – if applicable) in the 7 PAHO Region Reference NRAs (Argentina, Brazil, Canada, Colombia, Cuba, Mexico and United States) and the European Medicine Agency.

NRA	Status	
	Innovator	Generic
Argentina (ANMAT)	x	---
Brazil (ANVISA)	x	---
Canada (Health Canada)	x	---
Colombia (INVIMA)	x	---
Cuba (CECMED)	x	---
Mexico (COFEPRIS)	x	---
USA (FDA)	x	---
Europe (EMA)	x	---

8.2 PAHO Member State Prices

Through ECONMED (an electronic listserv for public officials from the health sector), PAHO requested the price paid for procurement of trastuzumab from Member States who utilize this products in their National Public Health Programs. Unfortunately, no data has been provided to PAHO by countries in Latin America and the Caribbean. PAHO will increase efforts to obtain some prices from Member States and will distribute the information when the committee convenes in Washington, D.C.

8.3 Results of PAHO Expression of Interest

For a medicine to be eligible for inclusion in the PAHO Strategic Fund medicine list, it must have supporting evidence of safety, efficacy, and clinical effectiveness. Additionally the product must satisfy one of the following criteria as related to the pharmaceutical market:

1. The acquisition of the medicines is subject to particular challenges related to product procurement, pricing, patent status, forecasting of future needs, and exclusivity contracts between pharmaceutical companies that restrict marketing in specific geographical areas.
2. Leveraging economies of scale (increases in the volume of medicine procured) can result in lower costs.

PAHO has established this criteria to ensure the inclusion of the product in the Strategic Fund will provide value added to Member States who procure this product through PAHO.

To evaluate these pharmaceutical market factors, the Procurement (PRO) Unit of PAHO conducted an Expression of Interest (EoI) to gather information related to the product. PRO contacted 19 suppliers, which are included in the PAHO approved supplier list, and asked for product data (i.e. available presentations, manufacturing origin & capacity, potential restrictions, prices, and available technical documents).

Trastuzumab is available through one manufacturer, Hoffmann La Roche, as there are no generic manufacturers producing this medicine. PRO did receive a response from Hoffmann La Roche and believes the product complies with the pharmaceutical market criteria mentioned above. As there is only one supplier for this product PRO recommends consolidating the regional demand to leverage the benefits of economies of scale. If PAHO is able to obtain sufficient demand perform an international tender and establish Long Term Agreements with Hoffmann La Roche.

8.4 Potential Value Added for Procurement of the Medicine through the Strategic Fund

The current version of the Strategic Fund medicine list, published in April of 2013, does not include any monoclonal antibodies for the treatment of breast cancer. If the presented evidence demonstrates adequate safety, efficacy, and clinical effectiveness, PAHO believes the inclusion of this product will improve Member States access to an effective and safe medicine that can be used to reduce the burden of breast cancer.

From an economic perspective, the elevated cost of this medicine may limit access in low and middle-income countries. Additionally, the product is only manufactured by one source (sole source provider), which can create additional barriers to access. If included in the Strategic Fund, PAHO would aim to consolidate regional demand to increase the Region's capacity to bargain with the sole source and obtain important cost reductions for Member States.

9. Search Strategy and References Supporting Intervention and Summary of Evidence

9.1 Inclusion Criteria

The aim of this evidence summary is to gather information from a systematic review about the benefits and risk of a drug in a specific health problem. For this reason we include in the summary the results from a rigorous systematic review, prioritizing Cochrane reviews. When a Cochrane review is not available or it is not suitable to respond the scope of the clinical question, we consider the inclusion of a systematic review that at least: i) includes a clearly defined inclusion criteria; ii) reports a recent search in at least two databases; and iii) reports any efforts from authors to assess the risk of bias from the included studies.

These criteria are the minimum requirements established by the Centre for Reviews and Dissemination to include a systematic review in the Database of Abstracts of Reviews of Effects (DARE; www.crd.york.ac.uk/crdweb/AboutPage.asp). For the specific purposes of the "Cost studies" section we include the results from an economic evaluation, that is; a comparison of two or more interventions or care alternatives (including cost-benefit analyses, cost-utility analyses, and cost-effectiveness analyses).

9.2 Search for Studies

The inclusion criteria described above determines the search for the studies planned. We design specific search algorithms to search the AHRQ Effective Health Care Program and The Cochrane Library as the main source to retrieve high quality systematic reviews. Each search in these two resources is complemented with a search in MEDLINE (accessed through PubMed) with the purpose of check any additional or more recent systematic review. The search is performed without any limitation, with the exception of PubMed in which we limit the search to the validated subset of systematic reviews (systematic[sb]). As we included only economic evaluations in the "Cost studies" section we limit the search to the NHS EED Database. In

those cases that the NHS EED Database does not provide relevant results, we perform a specific search in MEDLINE, limiting the search algorithm designed to retrieve systematic review with the term cost*[tiab]. The search to develop the present clinical question was performed in May 2013, with the search strategies detailed below (Section 9.5).

9.3 Rating the Quality of the Evidence

Each evidence summary provides a rating of the quality of evidence following the GRADE guidance. GRADE specifies four categories (high, moderate, low, and very low) that are applied to the body of evidence that supports each assessed outcome. In the context of a synthesis of the evidence the quality of evidence reflects the confidence that the estimates of the effect are correct. For each clinical question one experienced researcher collects in a table the number of studies and patients included in these studies that set the body of evidence for each specific outcome discussed in the "Benefits" and "Risks" sections. The quality of evidence is then rated for each specific outcome and a final category is provided, commenting the main limitations that compromise the quality of evidence. All the information collected in the table, and the details required to the rating of the quality of evidence are obtained from the assessed systematic review used to develop the evidence summary.

9.4 Selection Criteria

One experienced researcher screens the results from the search applying the inclusion criteria commented above. If a Cochrane review is identified, it is selected to develop the evidence summary. When a Cochrane review is not suitable to respond to the scope of the formulated clinical question, the references from MEDLINE are screened. For the purposes of this clinical question, no Cochrane reviews were available and from the 44 references obtained in MEDLINE we included two systematic reviews (*1,4*) that fulfilled with the inclusion criteria mentioned above. The revision of their title and abstracts led to the exclusion of the rest of references for not being focused in the metastatic stage of the disease, or for their design (original studies).

9.5 Search Strategy Results

The search to develop the present clinical question was performed in May 2013, with the following search strategies:

- **Agency for Healthcare Research and Quality – Effective Health Care Program**
  http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/

trastuzumab	0 hits

- **NHS Evidence**

trastuzumab AND breast AND HER2	672 hits
trastuzumab AND breast AND HER2 AND metastatic	513 hits

- **Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2013**

trastuzumab:ti,ab,kw	279 hits

- **MEDLINE (accessed via PubMed)**

1 trastuzumab[ti] AND breast[ti] AND systematic[sb]	44 hits
2 trastuzumab[ti] AND breast[ti] AND metasta*[ti] AND systematic[sb]	14 hits
3 1 OR 2	44 hits

9.6 References

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10. Additional References

The following references are those cited in Section 2 (Public Health Relevance), Section 4 (Medicine Characteristics and Pharmacological Information) and Section 8 (Special Considerations and Additional Comments). References supporting the intervention and summary of evidence are available in Section 9.6.

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