

# Medicines Information Bulletin

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## A Joint Inter-network Bulletin for Improved Decision-making

Working in a network is a strategy for coordination and exchange that brings together institutions and people who decide individually or in coordination to unite their efforts, experiences, and knowledge to achieve common goals. A network's members adopt organizational and management arrangements characterized by adaptability, flexibility, openness, collaboration, fluidity, and spontaneity in relationships.

The essence of working in a network is the decision of one or more people, institutions, or areas to carry out a common task, in pursuit of explicit shared goals, while maintaining the identity of the participants. It is equally important for the institutions and people that form the network to share specific interests and ideals.

Similarly, it should be noted that we live in an environment with a profusion of information on health and medicines, which offers very uneven quality. This environment is largely dominated by information

produced by the pharmaceutical industry, which can be strongly biased; therefore, independent information is a necessity. Information on medicines and therapeutics should be concise and practical, but also must provide the most relevant data on all pharmacological, clinical, and epidemiological aspects of medication use.

In this context and with the support of the Pan American Health Organization (PAHO), three regional networks focus their work on promoting better use of medicines by health workers and the public:

- Network Medicines Information Centers of Latin America and the Caribbean (CIMLAC Network).
- Regional Network of Drug and Therapeutics Committees (DTC Network).
- Network of Pharmacovigilance Focal Points (PV Network).

CIMLAC Network's mission is to link together the Medicines

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## Editorial

This first issue of the inter-network bulletin reflects the wish of all the members of the Network of Medicines Information Centers of Latin America and the Caribbean, the Network of Pharmacovigilance Focal Points, and the Regional Network of Drug and Therapeutics Committees to work together and create bonds of communication with each other and also with members of the health team in Latin America and the Caribbean to share information, viewpoints, and new developments on medicines and their rational use.

Our idea is to bring relevant information and news on medicines to our colleagues in the Region, making it possible, in principle, to strengthen the work of each network, while at the same time promoting optimization of the use of medicines by the societies in our Region.

The Network of Medicines Information Centers (CIMLAC Network) and the Network of Pharmacovigilance Focal Points (PV Network) have been developing and working for long enough to see the fruits of their labor. Even though the Regional Network of Drug and Therapeutics Committees (DTC Network) was recently formed, we are confident that it will become well established, carrying out the work it has planned for this year. We are also confident that the sum of the perspectives, positions, and growing capacity of each of the three networks separately will result in concrete benefits to health systems in Latin America and the Caribbean.

This issue provides relevant, timely information on medicines and shares and publicizes information on medicines alerts, suspensions, and withdrawals due to hazards. It emphasizes providing readers with a critical approach to the evaluation of medicines that are new on the pharmaceutical market, as well as those already in use but whose true role in therapeutics is not yet clear.

We look forward to receiving feedback from our readers, so that, together, we can improve this informative and educational bulletin.

Editorial Committee

### From page 1

Information Centers of Latin America and the Caribbean that are members of the network, respecting their autonomy. The network's main objective is to strengthen the Centers' role in the activities for which they were created. This includes providing independent active and passive information; collaborating on preparation of news media to support decision-making by health institutions, scientific organizations, universities, etc.; and functioning as a collaborative network for knowledge management in the field of medicines and therapeutics. More information on the network can be found at: <http://web2.redcimlac.org>

The main objective of the DTC Network is to facilitate setting up a tool for conceptual and methodological practical exchange on medicines evaluation at the regional level among national Drug and Therapeutics Committees (DTCs)

with the intention of contributing to the promotion of appropriate use of medicines. It also aims to facilitate cooperation among DTCs to optimize implementation of all their functions in the countries and help provide a database of evidence-based information on medicines used in the Region.

The objective of the PV Network is to integrate and strengthen the Region's medicines surveillance programs by promoting communication, effective collaboration among countries, information exchange, and knowledge generation about adverse events, problems affecting safety, and medicines use, in a public health policy framework. Participation in the network provides countries with the opportunity to access technical information, capacity building, and autonomy in case analysis and resolution, detection of signals from drug surveillance, and policy-making geared to appropriate medicines use.

This bulletin is a joint effort of the three networks. Its purpose is to provide useful information for better decision-making in health promotion efforts and appropriate drug use by health practitioners and the public.

The bulletin's objectives are:

1. Promote the rational use of medicines in Latin America and the Caribbean.
2. Facilitate dissemination of relevant information on efficacy, cost-effectiveness, safety (warnings and recalls), and prices available in the Region.
3. Promote critical thinking among health professionals around management of medicines information.

We invite you to be an active reader of this bulletin and to let us know if you have suggestions or observations about its content.

Please send your questions or suggestions to: [carlosfuentes@aisnicaragua.net](mailto:carlosfuentes@aisnicaragua.net)



# Medicines Information

## Therapeutic Positioning of Two Antiviral Combinations

(Evaluation by the Spanish Agency for Medicines and Health Products—AEMPS)

### 1. 1. Ledipasvir/sofosbuvir (Harvoni®)

March 2015

Infection with hepatitis C virus (HCV) is an enormous health problem in Europe especially in Mediterranean countries, where prevalence rates range from 1% to 3%. It is the leading cause of terminal liver disease and one of the main indications for liver transplant. Recurrence of the infection in the transplanted organ and a more aggressive and accelerated course make medium-term outcomes of liver transplant worse than those observed in cirrhosis from other etiologies.

At the time of this writing, the approved treatments on the

market for HCV infection are: pegylated interferon alfa (PEG); ribavirin (RBV); three NS3/4A protease inhibitors: boceprevir (BOC) and telaprevir (TVR), only effective on genotype 1, and simeprevir (SMV), effective on genotypes 1 and 4; sofosbuvir (SOF), NS5B nucleotide polymerase inhibitor; and daclatasvir (DCV), NS5A inhibitor, effective on all HCV genotypes.

Ledipasvir (LDV) is a specific NS5A protein inhibitor, essential for both RNA replication and for HCV virion assembly, used in combination with other medicines active against HCV.



LDV has been combined at fixed doses with SOF. On 17 November 2014, the European Medicines Agency (EMA) approved Harvoni®, the product of a fixed combination of LDV 90 mg/SOF 400 mg.

### AEMPS Conclusions

LDV/SOF is the first fixed-dose combination of two direct-acting antivirals; LDV, a specific NS5A protein inhibitor, and SOF, an NS5B nucleotide polymerase inhibitor.

In patients who have not received treatment (known as naïve patients) and pretreated patients that are candidates for treatment with interferon-free regimens, LDV/SOF represents a therapeutic alternative to other direct-acting antiviral combinations already authorized for HCV genotypes 1 and 4.

In select patients (with a viral load <6 million IU/ml) it also presents the advantage of being able to shorten treatment duration (8 weeks in naïve genotype 1 non-cirrhotic patients).

Coinfection with HIV does not negatively affect the activity of LDV/SOF.

According to data from the SOLAR-1 study, LDV/SOF + RBV for 12 weeks is an effective and safe therapeutic alternative in decompensated cirrhotic hepatitis C patients ineligible for IFN-based treatments.

LDV/SOF is not indicated in patients with genotype 2. Data on LDV/SOF in patients with genotype 3 are very limited.

At this time, the preferred regimen without interferon in pretreated patients without cirrhosis is DCV + SOF for 12 weeks.

In pretreated patients with genotype 3 with cirrhosis the optimal duration of LDV/SOF treatment is unknown; results point to considering that the combination LDV/SOF + RBV for 24 weeks can increase the sustained virological response (SVR) obtained with SOF +

RBV for 24 weeks. However, this has not been demonstrated. In these patients, LDV/SOF for 24 weeks would represent a therapeutic alternative to other regimens without interferon (SOF+RBV for 24 weeks or SOF/DCV for 24 weeks).

Although direct comparisons have not been made, from a clinical standpoint no IFN-free combination (12 weeks SOF+DCV, 24 weeks SOF+RBV) seems to be superior to 12 weeks SOF + PEG+RBV, which means that SOF + PEG/RBV for 12 weeks is the preferential guideline at this time whenever patients are likely to be susceptible to being treated with IFN.

LDV/SOF + RBV is an effective and safe therapeutic alternative in patients with recurrent post-transplant hepatitis C.

In patients without cirrhosis with mild to severe fibrosis (F0 to F3), in those with compensated cirrhosis (Child-Pugh A\*), and, possibly, in Child-Pugh class B patients with decompensated cirrhosis, prolongation of treatment from 12 to 24 weeks does not translate to an increase in the rate of SVR at 12 weeks. The small number of Child-Pugh class C patients in the SOLAR-1 study does not allow for conclusions on optimal treatment time with LDV/SOF + RBV (12 vs. 24 weeks) in this subgroup.

*\* Note: The Child-Pugh scale or classification is a scoring system used to evaluate the prognosis of chronic liver disease, mainly cirrhosis. It uses five clinical criteria for liver disease, each measured from 1 to 3, with 3 indicating the most severe damage.*

Complete report available at <http://bit.ly/1APIKgH>

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## 2. Viekirax® (ombitasvir/paritaprevir/ritonavir) and Exviera® (dasabuvir) March 2015

Viekirax® (OBV/PTV/RTV) and Exviera® (DSV) have been authorized, combined with each other or with other drugs, for treatment of hepatitis C. At present, the usual combination is OBV/PTV/RTV ± DSV ± RBV.

The drugs Viekirax® and Exviera® should not be used in

monotherapy. While they were being developed, small studies were conducted in combination with pegylated interferon.

At least one study is being conducted in combination with sofosbuvir (SOF) in patients with prior failure with other direct-acting antivirals (DAA).

No combination studies have been done with telaprevir, boceprevir, simeprevir, daclatasvir, or other similar molecules.

### AEMPS Conclusions

- The combination of OBV/PTV/RTV and DSV is the first authorized regimen without interferon that combines direct-acting antivirals and that does not include sofosbuvir.
- The regimen of OBV/PTV/RTV and DSV with RBV for 12 weeks is a therapeutic alternative to other DAA combinations in patients with genotype 1, both alone and coinfecting with HIV, with or without cirrhosis.
- In non-cirrhotic patients with genotype 1b, RBV can be dispensed with. In patients with genotype 1a and compensated

cirrhosis, with no response to previous treatment with PEG/RBV or factors predictive of poor response, prolonging treatment to 24 weeks is recommended.

- In patients with genotype 4, the regimen OBV/PTV/RTV with RBV administered for 12 weeks is a therapeutic alternative to other DAA combinations. However, in cirrhotic patients, the evidence comes from extrapolation of outcomes in patients with genotype 1b and optimal duration of treatment is unknown.
- In these cases, the recommendation is to use LDV/SOF (evidence still limited) or SMV/SOF, both for 12 weeks.
- According to preliminary data from the CORAL-I study, OBV/PTV/RTV and DSV + RBV for 24 weeks is an effective and safe therapeutic alternative in liver transplant patients with hepatitis C genotype 1, in which the disease recurs in a non-aggressive form and fibrosis is mild.
- The interaction profile of this combination should be taken into account, which complicates management of immunosuppression.
- In a post-transplant context, there are currently other combinations (SOF/LDV + RBV or SOF/SMV + RBV) that, with 12 weeks of treatment, obtain similar outcomes.
- In decompensated patients and/or those with advanced fibrosis, the lack of data with this combination makes the use of other therapeutic alternatives preferable.
- Data are not available on use of this combination in patients with HCV G1 with treatment failure with protease inhibitors or in patients with decompensated cirrhosis.
- Due to the presence of the protease inhibitor (PI) paritaprevir (PTV), use in patients with Child-Pugh C is contraindicated.
- There is no data in children, patients with kidney failure, and liver transplant patients with advanced fibrosis.
- The use of OBV/PTV/RTV and DSV is not indicated in patients with infection from genotypes 2 and 3. Both OBV/PTV/RTV and DSV cause interactions with other drugs that require their specific assessment.

Complete report at <http://bit.ly/19FbCBU>

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## Use of Chondroitin in Osteoarthritis Treatment

(Observations by network members on a systematic Cochrane review)

### Data insufficient to assign a place to chondroitin in treatment of osteoarthritis



Chondroitin is a drug widely used in numerous countries for treatment of osteoarthritis. A recently published systematic review evaluates efficacy and safety of oral chondroitin in osteoarthritis treatment compared with placebo or with active treatment (nonsteroidal anti-inflammatory

drugs, opioids, glucosamine, or other herbal medicines).

The paper's authors concluded that the review of randomized clinical trials, for the most part of poor quality, shows that chondroitin (alone or in combination with glucosamine)

is more effective than placebo in improving pain in participants with osteoarthritis, in short-term studies. The benefit was small to moderate with 8 points of improvement in pain (range 0-100) and 2 of improvement in the Lequesne index (range 0-24); both would seem clinically significant. These differences persisted in some sensitivity analyses and not in others. Chondroitin had a lower risk of serious adverse events compared to the control.

Although the combination of some efficacy and low risk

associated with chondroitin may explain its popularity among patients as an over-the-counter supplement, more high-quality studies are needed to explore the role of chondroitin in the treatment of osteoarthritis.

*Editor's Note: Considering that chondroitin is widely used for treatment of osteoarthritis, is important to emphasize the conclusion of the authors of this systematic review, since the majority of the studies included had few patients, were of limited duration, and had a high level of bias. The results of*

*the meta-analysis show a high degree of heterogeneity among the different studies, which decreases their reliability and weakens the level of evidence, which is low or moderate in the majority of cases. To date, the therapeutic place of chondroitin in the treatment of osteoarthritis cannot be concluded with these data.*

Reference: Singh Jasvinder A, Noorbalooshi Shahrzad, MacDonald Roderick, Maxwell Lara J. Chondroitin for osteoarthritis. Cochrane Database of Systematic Reviews: Reviews 2015; Issue 1.

Original abstract available at <http://bit.ly/1EiOrp9>

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## Information on Medicines Safety

### Diclorhexan 2%, High-dose Ibuprofen, and Hydrocortisone-induced Anaphylaxis

#### 1. CHILE: *Serratia marcescens* contamination of raw material in Diclorhexan 2% topical solution

On 10 November 2014, Chile's National Regulatory Authority (ANAMED) received a complaint reporting four cases of surgical site infection, with central venous catheter cultures and patients' blood cultures positive for *Serratia marcescens*. Additionally, positive cultures for the same bacterium were also obtained from different presentations and lots of the pharmaceutical product Diclorhexan 2% topical solution from DIFEM laboratories (Registry ISP No. F-18.108/10).

Subsequently, the Public Health Institute (ISP) tested samples, verifying that

the product was actually contaminated with the microorganism, and issued a resolution quarantining both the affected products and the raw materials used in their manufacture, as well as suspending distribution of the product.

Furthermore, it was decided to quarantine all products with chlorhexidine made by this laboratory, which would be effective while ANAMED finished testing needed to clarify in detail the origin of the contamination. In addition, the ISP recommended that health care providers discontinue



use of the products until the quarantine was lifted.

Notwithstanding the foregoing, DIFEM S.A.

laboratories, holder of the health registration, informed ANAMED that it had decided to withdraw other lots of the pharmaceutical product, since its own testing had found that part of the chlorhexidine gluconate, a raw material used in making these products, was contaminated with *Serratia marcescens*.

On 26 November 2014, the ISP ratified the total shutdown of DIFEM S.A. laboratories as a health measure, considering the following: the report from the health center that had filed the complaint, the records provided by the pharmaceutical company, the inspections by the ISP, and that the processes used for production and water were found to not be validated. In addition, it was confirmed that the supplier of the active ingredient, chlorhexidine gluconate 20%, was R.N. Laboratories PVT Ltd. from India. On 27 November 2014, as a health measure, the ISP ratified the withdrawal from the market of goods manufactured in this laboratory's production plant in view of the above and ruled that the findings confirmed by the inspectors made it possible to determine that the entire pharmaceutical production plant was contaminated by this enterobacterium. It also resolved that the measure would remain in effect until the company

demonstrably corrected the problem and that the laboratory's production facilities were free of contamination from pathogenic microorganisms.

It is noteworthy that in February 2015, the ISP was contacted by the AEMPS (Spanish Agency for Medicines and Health Products), which requested information on the case, and in turn reported the withdrawal of different products containing chlorhexidine because they were contaminated with *Serratia marcescens*. Ultimately, as the result of research conducted by the ISP, it was corroborated

that in both cases, the supplier of the raw material was R.N. Laboratories PVT Ltd. of India.

Finally, on 12 January 2015, the ban on distribution of pharmaceutical products made by DIFEM S.A. laboratories was partially lifted, for products made prior to the date that lots of the raw material chlorhexidine gluconate contaminated with *Serratia marcescens* were used, following verification of associated good manufacturing practices and negative results on microbiological quality control testing done on every series of the respective products.

#### Related Links of Interest:

1. Alert on withdrawal from the market of all pharmaceutical products made by DIFEM S.A. laboratories: <http://www.ispch.cl/comunicado/21487>
2. Quarantine order for the indicated product: <http://www.ispch.cl/resolucion/5808>
3. ISP ratifies total shutdown of DIFEM S.A. laboratories as a health measure:
4. ISP ratifies withdrawal from the market of goods manufactured in DIFEM S. A. laboratories pharmaceutical production plant as a health measure. <http://www.ispch.cl/resolucion/5912>
5. Alert on partial lifting of ban on distribution of pharmaceutical products made by DIFEM S.A. laboratories. <http://www.ispch.cl/comunicado/21653>
6. Withdrawal from the market of pharmaceutical compounds based on chlorhexidine made by Laboratorios Bohm, S.A., on or after 8 October 2014. [http://www.aemps.gob.es/informa/notasInformativas/cosmeticosHigiene/seguridad/2015/COS\\_01-2015-clorhexidina.htm](http://www.aemps.gob.es/informa/notasInformativas/cosmeticosHigiene/seguridad/2015/COS_01-2015-clorhexidina.htm)



## 2. Cardiovascular Risk from High Doses of Ibuprofen and Dexibuprofen: Recommendations for use

In April 2015, the EMA, AEMPS, and the other European national agencies reported<sup>1</sup> on the results of the overall assessment by the European Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA on the risk-benefit ratio (a European process known as “arbitration” or “referral”) of the cardiovascular risk of high doses of ibuprofen and dexibuprofen.

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) authorized for the treatment of mild to moderate pain, fever, and rheumatoid conditions and inflammation. Its mechanism of action is through nonselective inhibition of cyclooxygenase (COX), reducing prostaglandin synthesis. Dexibuprofen is the pharmacologically active S(+) dextrorotatory enantiomer of (racemic) ibuprofen and its uses are comparable, although they are not equipotent.

The PRAC has completed the review of cardiovascular (CV) risk associated with systemic administration of ibuprofen. This review is the continuation of previous reviews that concluded<sup>2</sup> in 2012 that use of NSAIDs in general is associated with a small increase in CV risk. This is a consequence of the withdrawal of rofecoxib (Vioxx®) in September 2004, due to cardiovascular risks<sup>3</sup>, and the withdrawal in February 2005 of valdecoxib because of serious cutaneous adverse reactions in addition to CV risk. Europe began a review of all NSAIDs,

and has been concluding with successive regulatory measures:

- Contraindications for the so-called coxibs (celecoxib, etoricoxib, parecoxib, valdecoxib) in patients with CV abnormalities that it concluded in June 2005.
- Evaluation of cumulative data on traditional NSAIDs, restricting ketorolac to hospital use; diclofenac at a dose of 150mg/day has been associated with an increase in risk of atherothrombosis, similar to that of some coxibs; and the last, recently, that high doses of ibuprofen show greater CV risk.

In addition, the PRAC has evaluated the potential interaction between ibuprofen/dexibuprofen and aspirin (acetylsalicylic acid) when the latter is administered at low doses in cardiovascular prevention.

The main conclusions have been the following:

- Data from clinical trials, observational studies, and meta-analyses confirm that administration of high doses of ibuprofen (at or above 2400 mg/day) are associated with an increased risk of arterial thrombosis, which is comparable to that of COX-2 inhibitors at standard doses.
- The available information suggests that doses of ibuprofen of up to 1200 mg/day, which are those



usually used as an occasional analgesic/anti-inflammatory or antipyretic, are not associated with increased cardiovascular risk.

- With regard to the potential interaction with aspirin, pharmacodynamic studies indicate that ibuprofen reduces the antiplatelet effect of aspirin. Although the epidemiological data available so far do not suggest that this interaction is clinically significant, the possibility that the cardioprotective effect of aspirin is reduced with regular and continuous administration of ibuprofen cannot be excluded.
- All the foregoing conclusions are equally applicable to dexibuprofen, taking into account that they are not equipotent and that 2400 mg of ibuprofen are equivalent to 1200 mg of dexibuprofen, exactly half (thus, 2.4 grams of dexibuprofen are equivalent to 4.8 grams of ibuprofen).

On 22 May 2015, the EMA published an update of the recommendations on the use of high-dose ibuprofen<sup>4</sup>, which confirmed the cardiovascular risk with doses at or above 2400mg per day.

To minimize the cardiovascular risk, high doses of ibuprofen (2400mg per day or higher) should be avoided in patients with underlying conditions, such as heart failure, heart disease, and circulatory problems, or in those who have previously had a heart attack or stroke.

In addition, it recommends that doctors should carefully assess a patient's risk factors before initiating long-term treatment with ibuprofen, particularly if high doses are required. Risk factors include smoking, high blood pressure, diabetes, and high blood cholesterol.

The recommendations for ibuprofen also apply to dexibuprofen. A high dose of dexi-

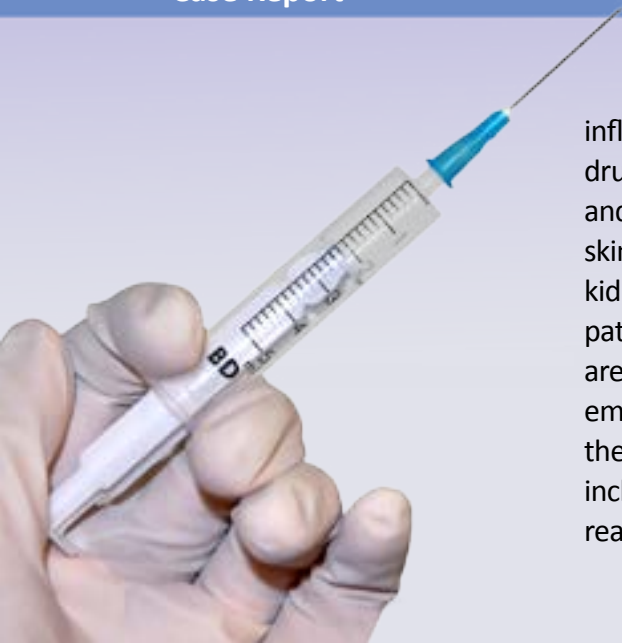
buprofen is a dose at or above 1200 mg per day.

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PV Network

### 3. Hydrocortisone-induced Anaphylaxis Case Report



Corticoids are powerful anti-inflammatory and antiallergic drugs used in patients of all ages, and in a range of diseases (allergic, skin, respiratory, rheumatologic, kidney) and even in transplant patients. For this reason, they are widely used in inpatient and emergency services. However their side effects are also known, including hypersensitivity reactions. Hypersensitivity to

corticosteroids is a complex phenomenon in which multiple factors interact, such as idiosyncrasy, intolerance, and allergy. A type IV hypersensitivity reaction, also known as a delayed hypersensitivity reaction, commonly occurs with topical corticoids; incidence is from 0.2% to 5%. On the other hand, immediate hypersensitivity (anaphylactic reactions)

occurs with the use of systemic corticosteroids; these are very rare, but can be fatal, and some authors have estimated its incidence from 0.1% to 0.3%.<sup>1</sup>

Here we present a rare case of anaphylaxis associated with the use of intravenous hydrocortisone.



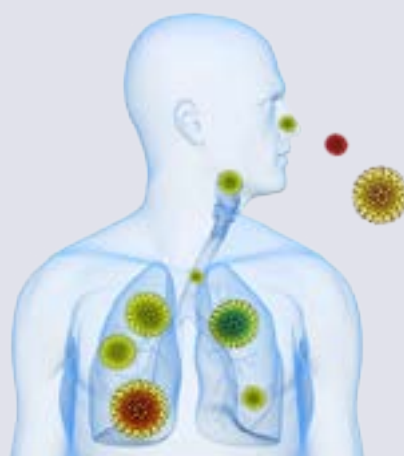
### Clinical case

The patient is a 10-year-old girl weighing 38 kg, with a history of rhinopharyngitis, bronchial asthma, and chronic tonsillitis, over a period of approximately 6 years. As part of her treatment, she repeatedly received prednisone, hydrocortisone, salbutamol inhaler, chlorphenamine, and antibiotics such as amoxicillin.

The patient was admitted to the hospital for surgery (tonsillectomy) with a diagnosis of chronic tonsillitis. On clinical examination, she did not have any major cardiovascular or pulmonary abnormalities. The pneumology evaluation found a pulmonary risk score of 2, which meant that hydrocortisone 100 mg was prescribed intravenously, 30 minutes before surgery, to prevent bronchospasms during surgery.

On the day of surgery, the patient awoke apparently normal, lucid, oriented in time and space, with 98% oxygen saturation,

heart rate of 80 beats per minute, respiration rate of 22 breaths/min, and temperature of 36.8 °C. She was given 50 mg diluted hydrocortisone by slow intravenous administration. Twenty minutes after administration of the drug, nurses found her pale, unresponsive to stimuli, with apnea, and cyanotic. Staff proceeded to carry out basic and advanced resuscitation maneuvers, in addition to the administration of adrenaline, without obtaining a response. Fifteen minutes later, the physician on duty confirmed the death of the patient from cardiac arrest. The results of the autopsy indicated that the cause of death was pulmonary edema and cerebral edema, attributed to a possible anaphylactic reaction from the use of hydrocortisone.



### Discussion

Immediate hypersensitivity reactions to parenteral glucocorticoids are rare, but often serious and potentially fatal; the prevalence of these reactions is from 0.2 to 0.5%.<sup>2</sup> Cases of anaphylaxis and anaphylactoid reaction have been reported with the use of systemic corticoids, characterized by skin rash, pruritus, severe headache, angioedema, obstruction of air flow, bronchospasm, respiratory

arrest, cardiac arrhythmia, hypotension, and anaphylaxis, which appear immediately after injection of the drug. This is a very complex phenomenon in which many factors interact, such as idiosyncrasy, intolerance, and allergic reactions. Some reports suggest that the allergenic component is due to the steroid itself and not to the excipients.<sup>3</sup>

The Swiss Drug Monitoring Centre SANZ detected 14 suspected hypersensitivity reactions that occurred from 1981 to 1999 in 13 patients immediately following parenteral administration of glucocorticoids. Nine of these cases were potentially fatal reactions: three patients experienced an acute asthma attack and six a serious anaphylactic reaction including shock. Risk factors were known in ten patients and were allergy, asthma, and hypersensitivity to aspirin.<sup>4</sup>

A case of corticoid-induced severe bronchospasm occurred in a 39-year-old patient, receiving dialysis therapy.<sup>5</sup> Potentially fatal reactions similar to anaphylaxis to intravenous hydrocortisone were described in patients with asthma.<sup>6</sup> Cases of hypersensitivity were reported in three children with asthma, aged 5, 7, and 8 years, who were administered intravenous methylprednisolone succinate in the emergency service.<sup>7</sup> There is some reason to believe that sodium succinate esters are more prone to causing a hypersensitivity reaction.<sup>8</sup> Pathogenesis is considered to be mediated by immunoglobulin E, in which the corticosteroid molecule serves as a hapten. In 2008 and 2011, a prospective study

was conducted that found that children with asthma and allergy to milk can have hypersensitivity reactions to the intravenous administration of sodium methylprednisolone succinate due to traces of milk protein from the lactose used as an excipient in the drug.<sup>9</sup>

An immediate hypersensitivity reaction to corticoids is usually associated with doses administered to male patients, and to patients with a history of asthma, kidney transplant, or who are hemodynamically unstable.<sup>10</sup> Our patient only received a 50 mg dose of hydrocortisone intravenously; however, the speed of drug infusion is unknown. In addition, the patient had a history of long-standing asthma, eventually using prednisone and intravenous hydrocortisone for management of exacerbations.

The recommendation for administration of systemic corticoids is to monitor the patient during and after drug administration and to pay attention to any manifestations of a suspected anaphylaxis reaction, especially in pediatric, asthma, and hemodynamically unstable patients.

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<sup>5</sup>Sirvent AE, Fernández I, Enríquez R, Alvarez JG, Santos Calle F, Samper J, Arenas MD, Reyes A. [Hypersensitivity reaction to systemic corticosteroids in a hemodialysis patients.] Nefrología: 2006, 26(1):128-131.

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<sup>7</sup>Nahum A1, Garty BZ, Marcus N, Shoenfeld T, Levy Y. Severe hypersensitivity reactions to corticosteroids in children. Pediatr Emerg Care. 2009 May; 25 (5):339-41



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# Network News

## Network of Pharmacovigilance Focal Points

### A. Coming Activities

#### Training On Analysis of Risk Management Plans



In September 2015, training on Analysis of Risk Management Plans will be given in Santiago, Chile by Dr. Gloria Giraldo of Health Canada. This training will be offered at no cost to

focal points in the Region's regulatory authorities.

For more information: [cglobos@ispch.cl](mailto:cglobos@ispch.cl), [vmvergara@ispch.cl](mailto:vmvergara@ispch.cl)

#### Regional Encounter of Pharmacovigilance

On 11-13 November, the XII Regional Encounter of Pharmacovigilance will take place in Medellín, Colombia. This event has grown stronger over

ten years, and in that time has addressed important technical/scientific and regulatory issues. In its early years, Colombia was the home of the event; however, it

was decided that the venue would alternate with other countries of the region every two years. In November 2014, Peru hosted the most recent conference.

### B. Current Projects

#### Development of Indicators for Evaluation of National Pharmacovigilance Centers

Since 2013, the PV Network has been working on an indicator tool for the evaluation of national centers based on international references (WHO, PAHO, USAID, etc.). At the last meeting of the

Network (Lima, 2014), the relevance and classification of the indicators were discussed, aimed at carrying out a pilot evaluation in Chile during the second half of 2015.

PAHO has supported the development of a manual for the evaluation and the results of the initial phase of this project will be discussed during the annual meeting in November (Medellín, 2015).

#### Multicountry Evaluation of Periodic Safety Update Reports (PSURs)



The Periodic Safety Update Report (PSUR) is a summary of up-to-date comprehensive information on the safety of a medicine, vaccine, or biotechnologic product, prepared by the marketing authorization holder, for the purpose of having data to evaluate the risk-benefit ratio for the life of the medicine on the market.

Given the need of regulatory authorities to evaluate these documents, the Network of

Pharmacovigilance Focal Points is preparing an instrument for evaluating PSURs, for the purpose of creating a tool that can guide evaluators from the national regulatory authorities in analyzing the information. Moreover, the goal is to evaluate these documents together among the countries of the Americas, with the aim of enhancing this activity in the countries of the Region, reducing duplication of efforts and promoting cooperation among countries.

## Network of Medicines Information Centers of Latin America and the Caribbean

### A. Coming Activities

#### VI CIMLAC Forum in Medellín, Colombia



The VI CIMLAC Forum is planned to take place in Medellín, Colombia on 11-13 November during the XII Regional Encounter of Pharmacovigilance.

A large number of country representatives are expected to attend along with as many representatives of member Centers as possible.

#### Validation of Medicines Information Centers Quality Indicators

Continuing an effort begun in 2014, a pilot test will be carried out with voluntary centers to validate the applicability

of the quality indicators for services provided by Medicines Information Centers. The goal of the network's members is to

publish the results in a Guide for Monitoring and Evaluation of Medicines Information Centers and Services.

### B. Current Projects

#### Medicines Evaluation Group

This year, CIMLAC network has reactivated the Medicines Evaluation Group for the purpose of evaluating medicines or molecular entities that have been approved for marketing by the health authorities of the Network's member countries in the last seven years. "Problem" medicines are also included, which are

medicines that, after being evaluated by health agencies from countries with high levels of health surveillance, were withdrawn from the market due to an unfavorable benefit/risk balance and are still marketed in Network member countries. This activity will receive support from members of the DTC Network in order to have

a broader evaluation of the medicines in question.

A working group is developing a procedures manual based on the international reference documents to adapt them to the Latin American region. It plans to evaluate a medicine of regional interest in 2015.

#### Regional Contact Database

Another effort begun in June 2014 by the Network is the creation of a regional database of contacts. This will consolidate a list of health agencies,

Ministries of Health, universities, and referral hospitals in each country with names, telephone numbers, and e-mails of key contacts. The database will make

it possible to raise awareness about the network at a broader level and disseminate relevant information on medicines to a greater number of people.

## Regional Network of National Drug and Therapeutics Committees

### A. Coming Activities

#### Training activities and development plan of action

The Regional Network of National Drug and Therapeutics Committees (DTCs) has been organized during the course of

this year. It conducted preliminary activities, starting with the call to health professionals who had participated in the online

courses on "Critical Information Analysis" aimed at DTCs of Latin America and the Caribbean. The courses were given by PAHO,

through the Centro Universitario de Farmacología (CUFAR) of the School of Medicine of the Universidad Nacional de La Plata. These courses were offered in 2010, 2011, 2012, and 2013. During the Network's preliminary activities, consensus was reached on objectives and target audiences, and experience sharing began.

One of the key strategies of the network is the evaluation of medicines and health technologies, for the purpose of providing information for decision-making by health authorities and

institutions. As a result, one of the main tasks of the network will be to build capacity in this regard in Latin American and Caribbean health professionals.

For 2015, the Network's plan of action includes three stages:

1. Taking a look at and characterizing the DTCs of LAC that integrate the network to identify strengths, gaps, and weaknesses in their makeup and operation.
2. Development of a reference document for the network—a

manual of procedures for DTCs.

3. Planning of activities taking into account the baseline situation of the different DTCs that emerges from the situation assessment.

CUFAR and PAHO have prepared an instrument for conducting the situation assessment of the committees.

## Pan American Health Organization

### Updated Model List of Essential Medicines for Adults and Children

At the 20th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines, in Geneva on 20-24 April 2015, the WHO Model List of Essential Medicines for Adults and Children was updated. This update added new treatments for hepatitis C, cancer (breast cancer and leukemia), and multidrug-resistant tuberculosis, among others, although several applications were rejected.

Five medicines (sofosbuvir, simeprevir, daclatasvir, dasabuvir, ribavirin) that seem to considerably improve the clinical condition of patients with HIV and hepatitis C were added. Medicines for the treatment of cancer have also been included that would produce considerable survival benefits, such as trastuzumab for breast cancer and imatinib for chronic myeloid leukemia and gastrointestinal stromal tumors.

Tuberculosis continues to be an infectious disease with high

mortality. In 2013, 1.5 million people died from this disease. After almost 45 years with very limited innovation in medicines to treat TB, five new medicines are now included, of which four target multidrug-resistant tuberculosis (bedaquiline, linezolid, delamanid, terizodone) and rifapentine for treatment of latent infection.

Furthermore, the Committee recommended excluding certain drugs, such as:

1. New oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, and apixaban to be used in stroke prevention in patients with atrial fibrillation without valvular injury. The committee did not find any relevant advantage to using these NOACs compared with the use of warfarin (vitamin K antagonists). It emphasized that more studies are needed to define the role that these NOACs can play in special circumstances in which



patients cannot be stabilized with warfarin.

2. Fixed-dose combinations (FDCs) for secondary prevention of cardiovascular disease. Several fixed-dose combinations had been presented for their inclusion in the cardiovascular drugs section of the WHO List of Essential Medicines. These formulations with different active ingredients in FDCs were presented: Aspirin 100 mg + simvastatin 40 mg + ramipril 2.5 mg, 5 mg, or 10 mg as an FDC; aspirin 100 mg + atorvastatin 20 mg + ramipril 2.5 mg, 5 mg, or 10 mg (another FDC); and

aspirin 100 mg + simvastatin 20 mg + atenolol 50 mg + hydrochlorothiazide 12.5 mg + ramipril 5 mg. The Committee recommended not accepting them based on the lack of evidence in relevant clinical variables, an increase in the number of adverse effects, and difficulties in titrating dosage when required by the clinical situation.

3. Ranibizumab. The Committee recommended not including ranibizumab for the treatment of proliferative eye diseases (with neovascularization) since the available evidence shows that it costs more without additional clinical benefits.

*Summary of the original press release (WHO <http://bit.ly/1JT-mWJI>) and observations added*

*by members of this Network based on: Executive Summary. The selection and use of essential medicines. Report of the 20th WHO Expert Committee on the Selection and Use of Essential Medicines. May 2015*

## Research

### Use of NSAIDs that Elevate Cardiovascular Risk

An Examination of Sales and Essential Medicines Lists in Low-, Middle-, and High-income Countries

**Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a widely used pharmacological group in our countries. It is worth asking: Do only cyclooxygenase 2 inhibitors present an increase in cardiovascular risk?**

This study investigated the level of evidence of cardiovascular risk associated with different NSAIDs and how knowledge of risk has led to orientation about and sales of these medicines in 15 low-, middle-, and high-income countries.

The 2013 study published in PLoS Medicine<sup>1</sup> found that medicines related to greater cardiovascular risk, compared to non-users of NSAIDs, were: rofecoxib (27% to 45% increase in risk), diclofenac (39% to 63%), and etoricoxib (53% to 105%). Naproxen was associated with the lowest risk (9%).

Diclofenac is on 74 national Essential Medicines Lists (EMLs), while naproxen is only on 27 of

them. Diclofenac and etoricoxib accounted for one third of total consumption of NSAIDs in the 15 countries studied (median 33.2%, range from 14.7% to 58.7%). Diclofenac was the most used, best-selling NSAID (mean 27.8%). Furthermore, naproxen had an average market share of less than 10%.

The authors concluded that the NSAIDs that are on EMLs should be those with an appropriate risk-benefit ratio, including those with lower cardiovascular risk. Thus for example, diclofenac has a risk very similar to rofecoxib, which was withdrawn from markets around the world due to its cardiovascular toxicity. However, many EMLs still include

diclofenac in the NSAID group instead of naproxen, which has a more favorable risk-benefit ratio.

Editor's Note: We agree with the conclusions of the authors and believe that diclofenac should be reserved for very specific use and for a short time in an injectable formulation.

#### Reference:

1-McGettigan P, Henry D. Use of Non-Steroidal Anti-Inflammatory Drugs That Elevate Cardiovascular Risk: An Examination of Sales and Essential Medicines Lists in Low-, Middle-, and High-Income Countries. PLoS Med 2013; 10(2): e1001388.

Original paper available at: <http://bit.ly/1LIsuYr>

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