



ANMAT

Administración Nacional de Medicamentos,
Alimentos y Tecnología Médica

INTERNATIONAL AND NATIONAL UPDATES ON MEDICINES SAFETY OCTOBER 2012

NEWS FROM INTERNATIONAL MEDICINES AGENCIES

AGOMELATINE (VALDOXAN®) – Antidepressant – Risk of hepatotoxicity.

(IMB, Ireland, October 11, 2012)

(ANSM, France, October 18, 2012)

Through a letter to professionals, Servier Laboratories informed about the risk of agomelatine-associated hepatotoxicity. It is also reported that among the cases observed, six patients presented with liver failure. Among other abnormalities found are: increased liver transaminases (up to ten times the normal value), hepatitis and jaundice that occurred more frequently in the first months of treatment. Liver injury appears to be mostly hepatocellular and laboratory tests values came back to normal after drug discontinuation.

The manufacturer recommends testing all patients taking the drug for hepatic function:

- Before starting treatment.
- Regularly at three, six, twelve and twenty-four weeks of treatment and thereafter.
- When the agomelatine dose is increased, respecting the same intervals as in treatment start.
- When clinically indicated.
- When a patient presents with increased transaminases, hepatic function must be monitored every 48 hours.

Agomelatine treatment should be discontinued if transaminases increase to levels three times higher than the normal ones and if signs or symptoms of liver injury appear, such as dark urine, hypocholia or acholia, jaundice, pain in the right upper belly, unexplained fatigue, etc.

Special precaution should be exercised on patients with increased transaminases prior to agomelatine treatment or with additional risk factors for presenting with hepatic failure (for example, obesity, fatty liver, diabetes or patients who take potentially hepatotoxic drugs).

<http://www.imb.ie/7334.htm>

<http://ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Valdoxan-agomelatine-Information-importante-de-pharmacovigilance-relative-au-risque-d-hepatotoxicite-Lettre-aux-professionnels-de-sante>

ANMAT recommends following the guidelines above mentioned. The National Pharmacovigilance System has received to date two spontaneous reports of agomelatine-associated hepatic disorders.

Agomelatine-containing products are within a risk management plan with a view to reinforcing the information provided to doctors about routine hepatic monitoring, to obtaining compliance with such monitoring by the doctor and the patient and to stimulating adverse event reporting.

Holders of marketing authorizations of agomelatine-containing products are reminded to update the information contained in patient information leaflets.

**DENOSUMAB – Osteoporosis treatment – Risk of symptomatic hypocalcemia.
(MHRA, United Kingdom, September 03, 2012)**

The medicine regulatory agency of the United Kingdom published a letter sent by the holder of the marketing authorization of Xgeva® (denosumab), addressed to professionals of health to warn about the risk of severe symptomatic hypocalcemia associated with the use of the above mentioned product that can occur at any time of treatment. Fatal cases have been reported.

<http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con185672.pdf>

ANMAT recommends watching for the occurrence of signs and symptoms of hypocalcemia in denosumab-treated patients (paresthesia, altered mental status, tetany, seizures and QT prolongation).

In order to minimize risks, health professionals are reminded to take into account the following recommendations when indicating therapy with this drug:

- **Pre-existing hypocalcemia must be corrected prior to the treatment with denosumab.**
- **Calcium and Vitamin D supplements must be indicated to denosumab-treated patients, unless hypercalcemia is present.**
- **If hypocalcemia occurs, the need for indicating an additional calcium supplement must be assessed.**
- **Patients with severe renal failure ($C_{Cr} < 30$ ml/min) and those dialyzed have an increased risk for hypocalcemia and therefore periodical monitoring for calcemia is recommended.**

The holder of the marketing authorization of this drug in Argentina informed about the risk of hypocalcemia at national level in August 2012.

Denosumab is within a risk management plan. The National Pharmacovigilance System has not received to date any report of hypocalcemia associated to this product.

**LENALINOMIDE – Treatment of multiple myeloma – Risk of second primary malignancies
(TGA, Australia, October, 2012)**

Lenalinomide is an immune modulator used in combination with dexamethasone for treating multiple myeloma. Clinical results of patients with multiple myeloma previously treated with this drug indicate a higher incidence of second primary malignancies, most of them, basal or squamous skin cells cancers.

FDA of the United States reported on this risk in **May 2012**.

<http://www.tga.gov.au/hp/msu-2012-05.htm#lenalidomide>

Holders of the marketing authorization of lenalinomide-containing products were requested (as per file 1-47-21684-11-8) to update patient information leaflets to include information about the risk of hypocalcemia and mandibular osteonecrosis.

PROTON PUMP INHIBITORS (PPI) – INTERACTION WITH METHOTREXATE – Increased side effects of methotrexate.

(Health Canada, Canada, October 19, 2012)

Through a communication addressed to health professionals, the Canadian agency announced that the information in PILs of methotrexate and PPIs will be updated to include information about a possible relevant interaction between both products. The concomitant use of these drugs can increase the amounts of methotrexate in the blood and, therefore, cause side effects, such as kidney failure, low blood red cell count, inflammation of the digestive tract, heart rate alterations, myalgias, infections and diarrhea.

Despite the fact that the association between the use of IPPs and the increase of methotrexate levels was not definitely confirmed, a series of studies suggests a probable potential increase of methotrexate-caused side effects.

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2012/2012_157-eng.php

Food and Drug Administration (FDA) of United States had already announced in **June 2012** that patient information leaflets of PPI-containing products would be updated to include the interaction with methotrexate.

ANMAT recommends:

- **Using PPIs at the lowest possible doses and for the shortest possible time, according to the specific pathology.**
- **Reporting any adverse event regarding the joint use of PPIs and methotrexate to the National Pharmacovigilance System.**

Holders of marketing authorizations of products containing proton inhibitor pumps as an active ingredient are reminded of the need to keep updated patient information leaflets.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) – Cardiovascular safety of traditional NSAIDs – The risk-benefit balance remains favorable.
(EMA, European Union, October 19, 2012)
(AEMPS, Spain, October 22, 2012)

The European medicines agency carried out a review of the latest scientific evidence about NSAIDs cardiovascular safety, which confirms the information provided in a previous review of 2006. That review concluded that the use of NSAIDs may be associated to an increased atherothrombotic risk.

In the current review, researchers concluded that the risk-benefit balance for these medicines remains favorable, even when diclofenac appears to have a higher atherothrombotic-type cardiovascular risk than ibuprofen and naxopren and remains under evaluation.

As to the rest of traditional NSAIDs, information is insufficient to draw conclusions.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/10/human_pha_detail_000067.jsp&mid=

http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2012/docs/NI-MUH_FV_15-2012.pdf

ANMAT recommends:

- **Using NSAIDs at the lowest efficacious doses and for the shortest possible time, taking into consideration the cardiovascular and gastrointestinal risks of each patient.**
 - **Prescribing and selecting NSAIDs on the basis of global safety profiles of each drug.**
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**SILDENAFIL – Inhibitor of cyclic GMP specific phosphodiesterase type 5 – Vasodilator.
(FDA, United States, August 30, 2012)**

Through a safety communication, the FDA in the United States recommended avoiding the use of sildenafil in children aged from 1 to 17 for treating pulmonary arterial hypertension.

This recommendation is based on the data provided by a recent clinical study carried out on a pediatric population in which researchers found the following:

- 1) children treated with this active pharmaceutical ingredient at high doses have a higher risk of death than those receiving it at a lower dose and that;
- 2) low doses of sildenafil were not associated to an improvement in exercising ability.

For all the above mentioned, labels will include the recommendation of not using sildenafil in children, even when it was never approved by the regulatory authority for treating pulmonary arterial hypertension.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm317743.htm>

ANMAT reminds holders of marketing authorizations of sildenafil-containing products to maintain patient information leaflets updated with the indications timely approved.

NATIONAL NEWS

BUPROPION (Wellbutrin XL®) – Antidepressant drug, noradrenaline and dopamine uptake inhibitor – Risk of congenital cardiovascular malformations.

Drug manufacturer GlaxoSmithKline has recently announced the results of an epidemiologic study that showed the existence of a potential increased risk of congenital cardiovascular malformations in newborns exposed to bupropion during the first quarter of pregnancy. Data suggest an increased risk of ventricular septal defects and of the left ventricular outflow tract.

Even when these data were not consistent throughout the different studies carried out so far on this topic, the above mentioned manufacturer will update the relevant sections in the patient information leaflets of its bupropion-containing medicinal products.

DEXTROPROPOXYPHENE – Risk of QT interval prolongation – Report by the Unit of Pharmacovigilance of the Second Chair of

Pharmacology of the School of Medicine of the University of Buenos Aires.

In February 2011, ANMAT commissioned the Second Chair of Pharmacology of the University of Buenos Aires School of Medicine with the implementation of a proactive pharmacovigilance program of dextropropoxyphene-associated QT prolongation, in the light of the United States FDA marketing suspension of that drug.

The Unit of Pharmacovigilance has sent preliminary data obtained from a study still in place carried out by the Chair within the framework of a UBACYT-granted fellowship. Information is summarized as follows:

- Out of the 1,270 patients included in the study in the period going from January 9, 2010 to June 01, 2012, 228 were treated with a dextropropoxyphene+dipirone association and 214 with a dextropropoxyphene+ibuprofen association, totaling 442 patients exposed.
- The dose used was never higher than 200 mg/day and treatment duration did not exceed 72 hours in any case.
- The relative Risk (RR) and the IC95 of presenting QTc>450 ms in men or higher than 470 ms in women, QTc>500 ms, Δ QTc>30 ms and Δ QTc>60 ms for each association was not statistically significant in any case.
- The data available suggest, as informed, that dextropropoxyphene at doses not higher than 200 mg/day and used for periods shorter than 72 hours have not shown to cause modifications in the QT interval that pose a significant risk for the generation of heart arrhythmias, which oppose the data published by the FDA in the MAD (Multi Ascending Dose) study.

<http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugafetyinformationforpatientsandproviders/ucm234330.pdf>

CLOZAPINE – Atypical antipsychotic – Treatment-resistant schizophrenia – Intensive Pharmacovigilance Program.

Clozapine is an atypical antipsychotic used for treating schizophrenia resistant to other medications, in schizophrenic patients with suicidal ideation or in those who have not tolerated the extrapyramidal side effects of other antipsychotics.

The most important and serious side effects associated to the use of clozapine are serious blood dyscrasias such as leucopenia, neutropenia and, in extreme cases, agranulocytosis with the consequent risk of infections. With a view to preventing such complication, an Intensive Pharmacovigilance Program is in place. Said program is carried out jointly with the four holders of marketing authorizations of clozapine-containing medicinal products (ANMAT Regulation 2534/96).

The above mentioned monitoring program includes a strict hematologic follow-up of all the patients undergoing a treatment with such active pharmaceutical ingredient. Patients to be treated with clozapine are to be enrolled in the various Intensive Pharmacovigilance Programs carried out by the holders of marketing authorizations of these products, who periodically report on the patients followed up and the hematologic alerts to the National Pharmacovigilance System.

ANMAT Regulation 935/00 set forth the updating of clozapine-treated patients monitoring program, to include the requirements for holders of marketing authorizations of these medicinal products. Likewise the informed consent form was updated and flow diagrams were added to implement the program both on outpatients and hospitalized patients, as well as an ongoing manufacturer monitoring program.

Comparative aspects of Pharmacovigilance/Intensive Pharmacovigilance

	Routine Pharmacovigilance	Intensive Pharmacovigilance (CLOZAPINE)
Medicines to which it is applied	All	Selected ones
Type of notification	Spontaneous	Mandatory
Type of adverse events	All	Serious and known
Patient informed consent	No	Yes

Doctors are reminded that:

- a) The use of Clozapine is forbidden in compounded preparations.**
- b) Their responsibilities as to the Program are the following:**
 - Giving patients a **clear explanation** of the possible **hematologic adverse events** associated to the clozapine treatment and its potential complications. Signing **two copies of the informed consent form** together with the patient or legal representative to enter the program.
 - Completing the **monitoring program enrollment application**, according to ANNEX IV of ANMAT Regulation 935/00. Every time the commercial brand of clozapine is changed, a new enrollment application must be signed as well as a treatment termination form (ANNEX V) for the commercial brand the patient had been receiving. The application must be signed in duplicate and a copy must be kept in the patient medical history and the other one must be sent to the clinical analysis laboratory.

- Instructing outpatients to go to the clinical analysis laboratory selected, with the enrollment application and the prescription for hematologic controls.
- **Prescribing the medicine, with the specification of the commercial brand**, issuing prescription(s) (in duplicate in case the patient acquires the medicine through their health maintenance organization), for which the hemogram showing results established as normal is to be submitted. The prescription **must bear the handwritten statement “normal hemogram” and the date of performance**.
- The doctor must issue the prescription for the hemogram corresponding to **the treatment stage, together with the prescription for the product**.
- If the patient is not post-hospitalization referred, the doctor must generate the **unique patient code**, which will be registered in the enrollment application. Said code will be made of the patient’s initial letter of the first name and the initial letter of the surname or first surname (or maiden name in case of married women) followed by the six digits of the birth date.
- If **hematologic adverse events** or any other event are detected during treatment, **the treating doctor must report them to the national health authority** by completing the corresponding pharmacovigilance form (yellow form). This action will be received **directly from the doctor or from the holder of the marketing authorization of the commercial brand of the medicine the patient is receiving**.
- In cases of **leucopenia/granulocytopenia**, the doctor must take an action in accordance to the **level of leucopenia**.
- Every time the patient discontinues a treatment, whether due to the change of the commercial brand, an adverse event, lack of efficacy, noncompliance with hematologic control, etc., the doctor must complete a **treatment discontinuation form**.

The following link contains detailed information about the regulatory framework of the Intensive Pharmacovigilance Program for clozapine-treated patients:

www.anmat.gov.ar/farmacovigilancia/Clozapina.asp

VACCINES

ROTAVIRUS VACCINES

Patel MM, Clark AD, Sanderson CFB, Tate J, Parashar UD (2012). “Removing the Age Restrictions for Rotavirus Vaccination: A Benefit-Risk Modeling Analysis”. PLoS Med (10):e1001330.doi:10.1371/journal.pmed.100133.

Rotavirus is the main cause of diarrhea in the world, mostly in infants and children younger than two years old. In our country, there are two types of vaccines approved by the national regulatory authority: the human monovalent vaccine G1 P 1[8] (Rotarix®) and the human-bovine pentavalent vaccine G1, G2, G3, G4 and P1 [8] (RotaTeq®), both of oral administration. Neither of them is included in the National Immunization Schedule yet.

An effective immunization against rotavirus is necessary because:

- The infection occurs both in developed and developing countries.
- An improvement in the environment hygiene does not control the infection.
- There is not an effective antiviral treatment.
- The higher mortality occurs in poor communities with a scarce medical coverage.
- This disease has a high family, social and economic impact.

Vaccination is intended to provide an immune response to the natural infection in order to:

- Protect against moderate/serious diarrhea.
- Prevent hospitalization and reduce mortality.
- Reduce socio-economic impact.

A research study carried out by the Center for Disease Control (CDC) and the London School of Hygiene and Tropical Diseases (LSHTM) evaluated the risks and benefits of removing the age restrictions recommended by the WHO for receiving the vaccine against rotavirus (first administration before 15 weeks of age and the last dose before 32 weeks). It was concluded that this change could save 50,000 more lives of children from low and medium income resources.

The age restrictions recommended by the WHO in 2009 were based on an adverse event (intestinal invagination) associated to the use of the first vaccine against rotavirus available in the United States (RotaShield®). However, according to the results of studies conducted in Finland, the United States and Latin America, such event was not observed with the use of other products marketed later on, such as Rotarix® y RotaTeq®.

<http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001330>