ANMAT
Administración Nacional de Medicamentos, Alimentos y Tecnología Médica

INTERNATIONAL AND NATIONAL NEWS ON DRUG PRODUCTS SAFETY JUNE 2012

INTERNATIONAL NEWS FROM REGULATORY AGENCIES

CANDESARTAN - Angiotensin receptor antagonist – Risk of fetal malformations.
(TGA, Australia, 06/2012)

The Australian drug agency reminds the public that both candesartan and other angiotensin receptor antagonists and angiotensin converter enzyme inhibitors are contraindicated in pregnancy as they can cause fetotoxicity. TGA received reports of fetal malformations in patients who used candesartan during pregnancy. Reports indicated renal failure, nephrocalcinosis, genito-urinary abnormalities, anhydramnios and renal dysplasia.

http://www.tga.gov.au/pdf/msu-2012-03.pdf

From 2004 to date, the National Pharmacovigilance System has received only one report of fetal exposure to angiotensin receptor antagonist. In this case, the patient was also receiving enalapril, furosemide and oxcarbazepine. All these drugs were early discontinued and the newly born baby had a low weight on birth without any other abnormality.

The risks associated with the use of angiotensin receptor antagonists and ACE during pregnancy are widely known. These drugs are contraindicated in pregnancy, and if the pregnant woman requires anti-hypertensives the treatment of choice must be non-teratogenic anti-hypertensives. Any fetal exposure to these drugs, regardless anatomical or functional malformations must always be reported to the National Pharmacovigilance System.

ZOLPIDEM – Non-benzodiazepine hypnotic – Sleep and amnesia related events.
(TGA, Australia, 06/2012)

The Australian drug agency has informed it continues receiving reports of zolpidem-associated amnesia, hallucinations and complex sleep-related behavior. From January 2009 to April 2012 the agency received 29 reports of sleep-walking, 27 of amnesia, 12 of hallucinations, 28 of abnormal sleep-related events, 7 of drug-dependence, 7 of abnormal behavior and 6 of car accidents.

http://www.tga.gov.au/pdf/msu-2012-03.pdf

From 2004 to date, the National Pharmacovigilance System has received one zolpidem-associated report of somnambulism, 3 of hallucinations, 2 of nightmares and 3 of disorientation.

ANMAT reminds the public that zolpidem, like all other non-benzodiazepine hypnotics, is to be sold under filed prescription only. Indications (short-term insomnia treatment), contraindications and precautions should be respected in order to reduce the occurrence of zolpidem-associated adverse events. It is essential to warn patients on the contraindications, precautions and adverse events related to this drug. Treatment should be discontinued on the appearance of any neuropsychiatric adverse event.

PROTON PUMP INHIBITORS - Anti-ulcer agents – Interaction with methotrexate.
(FDA, USA, 06/2012)

The US drug agency has informed it will change the labels of drug products containing proton pump inhibitors such as omeprazole, pantoprazole, rabeprazole and lansoprazole due to a significant interaction among the latter and methotrexate in high doses. When the latter inhibitors are administered concomitantly with methotrexate, the concentrations and/or metabolites of this immune-supressing and anti-neoplastic agent may be increased. This interaction has been observed in retrospective studies between methotrexate and proton pump inhibitors.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm306941.htm?source=govdelivery

Holders of marketing authorizations of drug products containing proton pump inhibitors as an active ingredient are hereby reminded of the need of keeping patient information leaflets updated. The Pharmacovigilance Department will keep on surveilling the interaction between methotrexate and proton pump inhibitors.

MINOCYCLINE – Tetracycline antibiotic – Use restriction.
(Afssaps, France, June 12, 2012)

The French drug agency has informed a use restriction for minocycline antibiotic due to the risk of serious and auto-immune hypersensitivity reactions. The use of minocycline is to be reserved for adults and children older than 8 years old for treating infections caused by sensitive bacteria, in the absence of another tetracycline or another antibiotic of the group with a better risk-benefit balance.

This review of the use of minocycline was triggered by the death of a young woman treated with minocycline who developed a serious hypersensitivity syndrome.

http://ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Minocycline-restriction-d-utilisation-en-raison-d-un-risque-de-syndromes-d-hypersensibilite-graves-et-d-atteintes-auto-immunes-Lettre-aux-professionnels-de-sante

From 2004 to date, the National Pharmacovigilance System has received 3 reports of urticaria, 1 of itching, 2 of angioedema and 3 of general skin rash associated with the use of minocycline. Out of these reports, two related to serious events. Regarding other tetracyclines, a report of tigecycline-associated skin erythema was received as well as another one of doxycycline-associated Stevens Johnson syndrome. ANMAT reminds readers that minocycline is an antibiotic indicated for serious infections caused by sensitive germs only when there is no other antibiotic available

with a better risk-benefit balance or in case of germs resistant to other groups of antimicrobials.

EMLA – Lidocaine-liprocaine patch – Risk of metahemoglobinemia.
(AEMPS, Spain, June 15, 2012)

The Spanish Pharmacovigilance System has reported 11 cases of metahemoglobinemia in patients treated with Emla on large skin surfaces. Emla is a drug product containing two anesthetics as active ingredients, such as lidocaine and prilocaine. Metahemoglobinemia is a clinical entity causing tissue hypoxia. Its main clinical sign is cyanosis which does not subside with high-flow oxygen. As it is an uncommon entity and clinical manifestations are non-specific, a high level of suspicion is required to reach the diagnosis.

http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2012/NI-MUH_FV_08-2012.htm

ANMAT recommends using EMLA according to the approved indications and doses. In Argentina, this drug product is marketed under dosage regimes lower than those approved in Spain. However, the risk of metahemoglobinemia remains mostly when when EMLA is used with other drug products that can increase metahemoglobinemia levels such as sulfonamides (sulfasalazine, sulfametoxasol), antimicrobials (chloroquine, dapsone, primaquine), nitrites and nitrates (nitroglycerin, nitroprusside) and others such as flutamide, phenobarbital, chinine and metoclopramide, among others.

File 1-47-11295-12-4 has been opened to request the holder of the marketing authorization to update the patient information leaflet.

FEBUXOSTAT – Hyperuricemia treatment – Risk of serious hypersensitivity reactions.
(MHRA, United Kingdom, May 18, 2012)
(Afssaps, France, June 15, 2012)

The French and English drug regulatory agencies spread data of a febuxostat safety review. Serious hypersensitivity reactions, such as anaphylactic shock and Stevens Johnson syndrome, were reported. Afssaps and MHRA will update febuxostat patient information leaflets.

http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON152832

http://ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Adenuric-R-febuxostat-Risque-de-survenue-de-reaction-d-hypersensibilite-grave-incluant-le-syndrome-de-Stevens-Johnson-et-des-chocs-anaphylactiques-aigus-Lettre-aux-professionnels-de-sante

ANMAT Pharmacovigilance Department has not received reports of febuxostat-associated serious hypersensitivity reactions. Serious hypersensitivity reactions such as anaphylactic shock and Stevens Johnson syndrome are known reactions of the drug, that occur most frequently during the first six-month period of treatment. Treatment must be suspended on the appearance of any skin reaction. Holders of marketing authorizations of febuxostat-containing drug products are reminded to keep updated patient information leaflets in the face of new safety matters.

TRIMETAZIDINE – Antiischemic – Risk-benefit balance review. (EMA, European Union, June 22, 2012)
(AEMPS, Spain, June 25, 2012)

The Committee on Human Medicinal Products (CHMP), a scientific committee of the European Medicines Agency, which is made up of representatives from all the European national agencies, has finished a review on trimetazidine risk-benefit balance. Conclusions are as follows:

Risk does not overweigh benefit for treating vertigo, tinnitus and visual field alterations.

In angina pectoris, trimetazidine should be used as an add-on treatment.
Trimetazidine should be contraindicated in patients with Parkinson disease, parkinsonism, shaking, restless leg syndrome or other movement disturbances, as well as severe kidney failure.

It should be carefully used in elder patients and those with moderate kidney failure. In these groups, treatment at a lower dose is recommended as trimetazidine accumulation may be greater.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/06/human_pha_detail_000063.jsp&mid=WC0b01ac058001d126

http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2012/NI-MUH_FV_11-2012.htm

ANMAT recommends:
- Not initiating new treatments with trimetazidine for treating vertigo or tinnitus.

- **Indicating trimetazidine for angina pectoris prophylaxis, as an add-on to other first-line treatments, when the patient is not adequately controlled or in case of intolerance to such treatments.**
- **Not indicating trimetazidine in patients with Parkinson disease, parkinsonism, restless leg syndrome and other movement disturbances as well as in patients with severe kidney failure.**
- **Discontinuing treatment in case of movement disturbances appearance.**
- **Reducing the dose in elder patients or those with moderate kidney failure.**

ANMAT reminds holders of marketing authorizations of trimetazidine-containing products of the need to keep updated patient information leaflets.

TOLPERISONE – Muscle relaxant – Risk-benefit balance review.

(EMA, European Union, June 22, 2012)

The European Medicines Agency has reviewed the efficacy and safety of tolperisone, which included the evaluation of clinical trials and post-marketing data such as adverse event reports. It was concluded that the trials conducted in the 1960s and 1970s do not comply with current standards and that there is only one study supporting its indication for spasticity occurring after a stroke. There is no sufficient evidence to support and approve other indications. On the other hand, half of the post-marketing adverse event reports are hypersensitivity-related, which outstrips the number of cases observed in the pre-market stage. For all the above, the EMA concluded that patient information leaflets should be updated to restrict the indication of tolperisone only to the spasticity occurring after a stroke and to highlight its hypersensitivity reactions.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/06/human_pha_detail_000062.jsp&mid=WC0b01ac058001d126

ANMAT Pharmacovigilance System has not received to date any tolperisone-associated hypersensitivity report. This Agency reminds holders of marketing authorizations of tolperisone-containing drug products of the need to keep updated patient information leaflets.

CEFEPIME – Fourth generation cephalosporin – Risk of convulsions and kidney failure.
(FDA, USA, June 26, 2012)

The FDA reminds professionals to adjust the doses of cefepime in patients with kidney failure, as some cases of non-convulsive status epilepticus have been reported. Moreover, cases of this adverse reaction in patients with kidney failure were less frequently reported. In such cases, patients had their doses adjusted based on creatinine clearance. Conditions resolved after cefepime treatment discontinuation or after hemodialysis. Cefepime dose should be adjusted in patients with a creatinine clearance lower that 60 ml/min. Ever since cefepime was approved in 1996 until February 2012, the USA drug agency received 59 reports of non-convulsive status epilepticus associated with the use of this antibiotic of which

56% occurred in patients older than 65 years of age (range: 7-95 years old); and in 58 of 59 cases, kidney failure was present and in most of them no dose adjusted had been performed.

http://www.fda.gov/Drugs/DrugSafety/ucm309661.htm

The National Pharmacovigilance System has not received to date any cefepime-associated non-convulsive status epilepticus report. The patient information leaflets of cefepime-containing drug products include the need for dose adjustment in case of kidney failure. Holders of marketing authorizations of this drug products are reminded to update patient information leaflets, particularly as to dose adjustment in the event of kidney failure, according to the above mentioned.

INTERNATIONAL NEWS ON POST-MARKETING STUDIES

BEVACIZUMAB – Treatment of macular degeneration – Risks as compared to ranibizumab.

Sanjay Sharma et al. Rate of serious adverse effects in a series of bevacizumab and ranibizumab injections. Canadian Journal of Ophthalmology. 2012; 47 (3); 275-279.

This is retrospective cohort study on patients who received bevacizumab or ranibizumab via the intraocular route. Topical and systemic adverse events occurred after one month of application. As to the demographic characteristics of each population, there were not statistically significant differences between number of patients, gender and indication for application. Ranibizumab-treated patients were 1.8 older than those treated with bevacizumab (78.7 vs 76.9, $p<0.01$) and their visual acuity was greater before the application. Acute intraocular swell occurred as an adverse event in 9 cases of bevacizumab administration and in 1 of ranibizumab administration (odds ratio: 11.71; interval of confidence 95%: 1.5-93.0). No other ocular adverse events occurred one month after the injection. Regarding systemic adverse events, 3 patients who received bevacizumab experienced arterial thromboembolic events (two of them acute myocardial infarction and one transient ischemic attack), whereas only one ranibizumab-treated patient had the transient ischemic attack event. In this regard, there is an increased tendency by the bevacizumab group to experience thromboembolic

events, with a 4.26% odds ratio, but with an interval of confidence of 95% of 0.44 a 41.

http://www.canadianjournalofophthalmology.ca/article/S0008-4182(12)00143-3/abstract

This study has certain constraints and therefore result interpretation should not be categorical. Regarding design, this is a retrospective study with bevacizumab and ranibizumab not administered in the same period (June 2006 - March 2008 for bevacizumab and March - September 2008 for ranibizumab). On the other hand, there may be some constraints in terms of data input in clinical records. As to arterial thromboembolic events, the article does not make any reference to significant underlying conditions, such as a previous acute myocardial infarction, diabetes mellitus or other cardiovascular diseases that might have increased the cardiovascular risk in these patients. In spite of the above, the study shows that bevacizumab is associated with a higher rate of adverse events, both topical and systemic, as compared to ranibizumab.

ANMAT reminds the public that bevacizumab has not been approved in our country under an intra-ocular application dosage form. The only route of administration approved to date is the intravenous route.

NATIONAL NEW

CERVARIX – Vaccine against human papilloma virus – Scheduling errors.

The National Pharmacovigilance system has received reports of scheduling errors associated to the use of Cervarix vaccine, indicated against human papilloma virus. The reports account for 6 cases in which the interval between the second and the third doses was disregarded. Readers are reminded that the administration schedule for this three-dose vaccine is 0, 1 and 6 months. This vaccine is indicated for female population from the age of 10 years onwards. However, Cervarix and Gardasil, another approved human papilloma virus vaccine, have alternative administration schedules.

Cervarix and other vaccines patient information leaflets can be checked by inquiring ANMAT Drug Formulary.

http://www.anmat.gov.ar/aplicaciones_net/applications/consultas/vademecum/vademecum.asp