ANMAT
Administración Nacional de Medicamentos, Alimentos y Tecnología Médica

INTERNATIONAL AND NATIONAL NEWS ON DRUG PRODUCTS SAFETY - SEPTEMBER 2012

INTERNATIONAL REGULATORY AGENCIES

TOPICAL ANALGESICS – Risk of serious burns
(FDA, United States, September 13, 2012)

Food and Drug Administration (FDA) warned, through a safety communication, about the risk of chemical burns (that may range from first-to-third degree burns) with the use of over-the-counter topical pain relievers for muscle and joint pain, containing menthol, methyl salicylate or capsaicin (as single or combination ingredients). Normally, when applied to the skin, these products should not cause pain or tissue injury; however, rare cases of serious burns have been reported, even after one single application.

http://www.fda.gov/Drugs/DrugSafety/ucm319339.htm

The National Pharmacovigilance System has not received to date any report on skin burns following the use of menthol, salicylate or capsaicin containing products. Patients using any products of this type and having signs of injury in the application site, such as pain, swelling or blistering should discontinue its use and seek immediate medical help. Holders of marketing authorizations of menthol, salicylate or capsaicin containing products are to update the information contained in patient information leaflets.

DONEPEZIL – Treatment of dementia of the Alzheimer type – Risk of neuroleptic malignant syndrome.

(EMA, European Union, July 2012)
(IMB, Ireland, August 2012)

Donepezil is a reversible acetyl-cholinesterase inhibitor used for treating dementia associated to Alzheimer's disease. The EMA (European Medicines Agency) Pharmacovigilance Working Party (PhVWP) reviewed the risk of serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) associated with the use of this drug. The reviewing group has not found sufficient evidence of a causal relationship between the use of this drug and SS, as no pre-clinical studies data were available. Only a few spontaneous reports were found and all of them involved the concomitant use of other drugs capable of having caused the syndrome. Nevertheless, a possible causal relationship was informed between the use of donepezil and NMS occurrence, both when used as a single drug and associated to other drugs, generally, antipsychotics. Factors suggesting this association include positive dechallenge, the plausible temporal relationship with the administration and the occurrence of symptoms after a dose increase.

http://www.emea.europa.eu/docs/en_GB/document_library/Report/2012/07/WC500130391.pdf

http://www.imb.ie/images/uploaded/documents/Drug%20Safety%20Newsletter%2049%20final%20hyperlinked.pdf

From 2004 to date, the National Pharmacovigilance System has not received any donepezil-associated NMS report. A WHO Uppsala Monitoring Center database query retrieved 19 reports of donepezile-associated NMS reports in subjects treated with donepezil from 1999 to present; none of the patients had received donepezil as a single drug and, in most cases, it had been combined with antipsychotics. Of the 19 cases, two were evaluated as possible and one as probably related with the use of donepezil; whereas the causality of the remaining cases was not informed. Donepezil treatment discontinuation is recommended on occurrence of signs or symptoms indicative of NMS (hyperthermia, muscle rigidity, altered consciousness, autonomic instability, increased CPK, etc.) or fever unexplained by other causes without other NMS manifestations.

PRAMIPEXOLE – Dopamine agonist for treating Parkinson´s disease - Risk of heart failure.
(FDA, United States, September 09, 2012)
United States Food and Drug Administration (FDA) has communicated that recent studies suggest a potential risk of heart failure associated to the use of pramipexole. US regulatory agency reviewed data of randomized studies and found that heart failure was more frequent in pramipexole-treated patients than in placebo-treated patients; but, results were not statistically significant. Likewise, two epidemiologic studies were reviewed and they revealed an increased risk of heart failure in pramipexole-treated patients. However, certain limitations of these studies do not allow for final conclusions.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm320054.htm

To date, the National Pharmacovigilance System has not received any report on heart failure in pramipexole-treated subjects. From 1998 to present time, WHO Uppsala Monitoring Center database has contained 48 reports of heart failure in pramipexole-treated patients, of which, only 9 received the drug as a single treatment and only 3 cases were evaluated as possibly caused by pramipexole. In this regard, ANMAT recommends:

☐ To tell patients to see a doctor in case of heart failure symptoms.

☐ To weigh the risk and benefit for each individual patient when prescribing pramipexol.

☐ To report pramipexol-associated heart failure events to the National Pharmacovigilance System.

INHIBITORS OF DIPEPTIDYLPEPTIDASE-4 (DPP-4) – Vildagliptin, saxagliptin, sitagliptin, linagliptin – Type 2 diabetes treatment – Risk of acute pancreatitis.
(MHRA, United Kingdom, September 2012)
The United Kingdom drug regulatory agency informed an increased risk of acute pancreatitis associated with DDP-4 enzyme inhibitors treatment for glycemic control in type 2 diabetes patients.
Most cases were identified through spontaneous reports in post-marketing stage of the drugs of this group. Even when the occurrence of this event appears to be low

(between 1/1000 and 1/100 patients receiving the drug), the exact frequency is unknown due to the few cases reported in clinical studies.
It is important to bear in mind that diabetic patients have an increased risk for pancreatitis associated to the metabolic disease itself.

http://www.mhra.gov.uk//Safetyinformation/DrugSafetyUpdate/CON185628

Products currently marketed in Argentina are as follows:
Galvus (vildagliptin) – Novartis
Galvus Met (vildagliptin +metformin) – Novartis
Janumet (sitagliptin + metformin) – Merck, Sharp & Dohme
Januvia (sitagliptin) - Merck, Sharp & Dohme
Kombiglyze XR (saxagliptin+metformin) – Bristol-Myers Squibb
Onglyza (saxagliptin) – Bristol-Myers Squibb
Trayenta (linagliptin) – Boehringer Ingelheim
Zomarist (vildagliptin) – Montpellier
Zomarist Met (vildagliptin+metformin) – Montpellier

In March 2012, the French drug regulatory agency, ANSM, communicated the risk of pancreatitis associated with the use of saxagliptin.
The National Pharmacovigilance System has received so far two reports of acute pancreatitis in saxagliptin-treated patients.
Linagliptin, saxagliptin, vildagliptin and the combination of vildagliptin and metformin are currently included in risk management plans.
Holders of marketing authorization of these medicinal products are reminded of the importance of keeping updated patient information leaflets.

LEVODOPA AND OTHER DOPAMINE AGONISTS – Treatment of Parkinson´s disease – Risk of impulse control disorders.
(EMA, European Union, July 2012)
(IMB, Ireland, August 2012)

Dopamine agonists, including levodopa, cabergoline, bromocriptine, pergolide, lisuride, pramipexol and apomorphine are drugs mainly indicated as replacement therapy in patients with Parkinson´s disease. A review of published data carried out by the European Medicines Agency (EMA) Pharmacovigilance Working Party (PhVWP) informed that patients treated with dopamine agonists at usual doses and independent from indication have an increased risk of impulse control disorders, that may present with a variety of symptoms including pathological gambling, hypersexuality, libido increase, compulsive buying and binge eating, among others.

http://www.emea.europa.eu/docs/en_GB/document_library/Report/2012/07/WC500130391.pdf

http://www.imb.ie/images/uploaded/documents/Drug%20Safety%20Newsletter%2049%20final%20hyperlinked.pdf

To date, the National Pharmacovigilance System has only received one report of pathological gambling possibly related to ropirinol.
Health care professionals are recommended to regularly monitor the occurrence of impulse control disorders in patients treated with dopamine agonists. Both patients and care givers should be aware of the symptoms associated with these disorders and report them to health care professionals if they occur. Holders of marketing authorizations of

dopamine agonists are reminded of the need to keep data updated in patient information leaflets.

INTERNATIONAL UPDATES ON POST-MARKETING STUDIES

ATAZANAVIR – Treatment of HIV infections – Risk of renal lithiasis.

Yohei Hamada et al. National Center for Global Health and Medicine. Tokyo, Japan. Presented on September 10, 2012 at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held in San Francisco, California.

According to a recent study, atazanavir-treated patients are ten times more prone to present with renal lithiasis than other patients treated with other protease inhibitors. This study compared a group of 465 atazanavir-treated HIV-infected patients with another group that included 773 patients who received other protease inhibitors, from January 2004 to June 2010. Renal lithiasis was diagnosed in 31 of the atazanavir-treated patients and only in four subjects receiving other protease inhibitors. Of the 18 patients who continued to receive atanazavir treatment, six had a relapse of the adverse event; whereas none of the patients who discontinued the drug, had renal lithiasis again.

http://www.medscape.com/viewarticle/771421?src=emailthis

ANMAT recommends:

To use atazanavir cautiously in patients with kidney failure or renal lithiasis predisposing factors.

To assess, on an individual basis, the benefit of continuing to administer this drug to subjects with a history of renal lithiasis due to the risk of a relapse.

To report any case of renal lithiasis in atazanavir-treated patients to the National Pharmacovigilance System.