ANMAT
Administración Nacional de Medicamentos, Alimentos y Tecnología Médica

INTERNATIONAL AND NATIONAL NEWS ON DRUG PRODUCTS SAFETY – APRIL 2012

INTERNATIONAL DRUG REGULATORY AGENCIES

DARIFENACIN – Anti-cholinergic – Effects on the central nervous system. (FDA, USA, MARCH 2012)

The USA drug regulatory agency reported the notification of several adverse effects on the central nervous system such as headache, confusion, hallucinations and somnolence related to the use of darifenacin, an anti-cholinergic indicated for treating over-reactive bladder. These effects were observed at the beginning of treatment and/or upon dose increase.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm233702.htm

The National Pharmacovigilance System has not received any of above mentioned darifenacin adverse event reports. Darifencin-containing drug products currently marketed in Argentina are the following:

- **Continex by Baliarda pharmaceutical company.**
- **Darisec by Elea pharmaceutical company.**
- **Enablex by Novartis pharmaceutical company.**

This Administration recommends:

- **Warning patients that they should not drive vehicles or use heavy machinery until darifenacin is determined to cause central nervous system effects.**
- **Suspending treatment if adverse reactions such as confusion, hallucinations and somnolence occur.**

Furthermore, file 1-47-7190-12-7 has been opened to request holders of the above mentioned drug products to update the adverse reactions section in patient information leaflets.

NITROFURANTOIN – Antibacterial agent – Use restrictions.
(Afssaps, France, March 12, 2012)

The French drug regulatory agency has reevaluated the risk-benefit balance of nitrofurantoin-containing drug products and announced new use restrictions. Such restrictions are: cystitis treatment in persons over 6 years old, when no other antibiotic with a better risk-benefit balance is available. Repeated treatment should be avoided due to serious allergic reactions, except for recurrent urinary infections caused by multi-resistant bacteria. Still, nitrofurantoin should be used for prophylaxis for recurrent urinary tract infections.

http://www.afssaps.fr/Infos-de-securite/Lettres-aux-professionnels-de-sante/Nitrofurantoine-Restriction-d-utilisation-en-raison-d-un-risque-de-survenue-d-effets-indesirables-graves-hepatiques-et-pulmonaires-Lettre-aux-professionnels

Since 2004, ANMAT has been reported on 13 adverse events occurred with nitrofurantoin-containing drug products. Three of said reports relate to skin reactions (none serious) and five to respiratory disorders, out of which one was serious. None of the above mentioned reactions occurred in pediatric patients; however, only one digestive intolerance-related adverse reaction was reported in a 6-year-old patient.

File 1-47-7191-12-0 has been opened to request holders of marketing authorizations of nitrofurantoin-containing drug products to include the information above in the indications section in patient information leaflets.

CITALOPRAM – Antidepressant – QT interval prolongation.
(FDA, USA, March 28, 2012)

In August 2011, the FDA reported a higher risk for QT interval prolongation associated with the use of citalopram at doses greater than 40 mg/day. In December 2011 the United Kingdom drug regulatory agency warned about the same fact. In March 2012, the USA drug regulatory agency announced that patient information leaflets of citalopram-containing drugs had been revised to include new precautions and recommendations for use.

Patients with congenital long QT syndrome have a high risk for *Torsade de Pointes*, ventricular tachycardia and sudden death. However, citalopram is not contraindicated in these patients as they may benefit from a low-dose treatment, where there is no therapeutic alternative available.

Citalopram is not recommended for patients with recent myocardial infarction, uncompensated heart failure and electrolyte disturbances such as hypokalemia and hypomagnesemia.

The maximum dose recommended for patients older than 60 years is 20 mg/day. Treatment should be interrupted when a QT interval longer than 500 ms is detected.

Special caution should be taken with patients using concomitant drugs that prolong the QT interval or inhibitors of the cytochrome system since citaloprom concentrations may be increased in such cases.

http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm

In August 2011, holders of marketing authorizations of citalopram-containing drugs were requested to revise patient information leaflets to include these new precautions and recommendations of use (file 1-47-16396-11-3). ANMAT recommends taking the precautions and following the indications above mentioned.

PROTON PUMP INHIBITORS – Anti-ulcer drugs – Hypomagnesemia.
(MHRA, United Kingdom, April, 2012)

According to a drug safety update by the United Kingdom drug regulatory agency, severe hypomagnesemia associated with the use of proton pump inhibitors (PPI) has been infrequently reported.

Some cases occurred in the third month of treatment but most cases appeared after one year approximately.

Therefore, patients on prolonged treatment with IIP or taking digoxin or other hypomagnesemia causing drugs (e.g. diuretics) should have magnesium periodically measured during treatment.

http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON149774

In March 2011, the USA drug regulatory agency, FDA, published a safety announcement about the association of proton pump inhibitors with hypomagnesemia. Our National Pharmacovigilance System has not received any reports of hypomagnesemia associated with PPI but this can be due to the lack of knowledge of the hypomagnesemia-PPI association. It should be noted that PPI-containing drug products are sold over the counter. This Administration recommends:

- **Measuring magnesium periodically in patients on IPP prolonged treatment and/or who take hypomagnesemia-causing drugs.**
- **Patients who take unprescribed (over-the-counter) PPI should not prolong the treatment beyond two weeks. If digestive symptoms do not subside, patients should see a doctor.**

STRONTIUM RANELATE – Osteoporosis treatment – Risk for thromboembolism and serious hypersensitivity. (Afssaps, France, March 4, 2012)

In March 2012, The European Medicines Agency´s Committee for Medicinal Products for Human Use and the Spanish Agency for Medicines and Health Products informed about the risks of thromboembolism and serious hypersensitivity associated to the use of strontium ranelate.

In April, the French drug regulatory agency warned about these risks and affirmed that strontium ranelate keeps a favorable risk-benefit balance and maintained the indication for use in post-menopausal women with osteoporosis.

http://www.afssaps.fr/Infos-de-securite/Points-d-information/Protelos-R-ranelate-de-strontium-nouvelles-contre-indications-afin-de-minimiser-le-risque-thrombo-embolique-veineux-apres-la-reevaluation-europeenne-Point-d-information2

This Administration reminds readers that last March holders of marketing authorizations of strontium ranelate-containing drug products were requested to update patient information leaflets to include these recently found risks (file 1-47-5668-12-7). The drug products containing the above mentioned drug are the following:

- **Osteovital by Investi pharmaceutical company.**
- **Prodinam by Astra Zeneca pharmaceutical company.**
- **Protos by Servier pharmaceutical company.**
- **Troncel by Roux Ocefa pharmaceutical company.**

BENZOCAINE – Local anesthetic – Risk of metahemoglobinemia. (Health Canada, Canada, May 4, 2012)

In April 2011, the Canadian drug regulatory agency and the FDA warned about the risk of metahemoglobinemia associated with the use of topic benzoncaine. In April 2012, the Canadian agency announced that patient information leaflets of benzocaine-containing drug products would be changed to add the risk of metahemoglobinemia and the importance of using the lowest possible dose as well as guidance for the recognition of this disease symptoms and signs.

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2012/2012_52-eng.php

The concentrations of benzocaine in the drug products marketed in our country are lower than those in the United States and Canada.

The National Pharmacovigilance System has not received any metahemoglobinemia case report. ANMAT reminds readers that these drug products are sold over the counter and that they should be used for the shortest possible time and at the lowest doses.

DROSPIRENONE – Oral contraceptive – Risk of thromboembolism (FDA, USA, April 10, 2012)

The FDA has finished a review of epidemiologic studies on the risk of thromboembolism in women treated with drospirenone. Based on said review, the American agency has concluded that drospirenone-containing birth control pills carry an increased risk for thrombotic events as compared to other contraceptive drugs.

The studies reviewed do not provide consistent estimators as to the comparative risk of thrombosis in birth control pills with or without drospirenone. Moreover, these studies neither considered characteristics of patients that could have an influence on prescription and that could affect the risk of thrombosis. Therefore, it is not clear whether the increased risk observed is solely due to drospirenone.
Consequently, the FDA ordered information for patients to be updated with the indication that some epidemiologic studies showed an increased risk of thrombosis whereas other studies did not prove an additional risk in drospirenone-containing drug products.

http://www.fda.gov/Drugs/DrugSafety/ucm299305.htm

During 2011, within the framework of ANMAT Observatory, this agency held meetings with Sociedad de Obstetricia y Ginecología de Buenos Aires (SOGIBA), Asociación Médica Argentina de Anticoncepción (AMADA), Sociedad Argentina de Endocrinología Ginecológica y Reproductiva (SAEGRE), Sociedad Argentina de Ginecología Infanto-Juvenil (SAGIJ) and Federación Argentina de Sociedades de Ginecología y Obstetricia (FASGO). It was concluded that each patient´s risk for thrombosis should be evaluated and the risk-benefit balance for indicating the drug should be considered before indicating drospirenone.

Based on the current medical evidence, ANMAT will request the update of patient information leaflets of drospirenone-containing drug products and the addition of other relevant information.

ALISKIREN – Renin inhibitor – New contraindications and warnings. (FDA, USA, April 20, 2012)

January and February "Pharmacovigilance News" reports informed that the drug regulatory agencies of Spain, Canada, the United Kingdom and the European Union had announced the re-evaluation of Aliskiren risk-benefit balance. Such re-evaluation was due to the disruption of Altitude, a clinical trial in which cases of ictus, renal complications, hyperkalemia and hypotension were reported in Aliskiren-treated patients as compared to placebo-treated patients.

The above mentioned agencies reviewed the risk-benefit balance and introduced new restrictions for the use of Aliskiren combined with angiotensin enzyme converter (ACE) inhibitor and angiotensin II receptor blockers (ARB).

The combined use of Alikiren with ACEs or ARBs is contraindicated in diabetic patients and in those with moderate or serious renal failure, whereas such combination is not recommended for the rest of the patients. The FDA will update patient information of Aliskiren-containing products.

http://www.fda.gov/Drugs/DrugSafety/ucm300889.htm?source=govdelivery

ANMAT has already started procedures for updating patient information leaflets with these new contraindications and warnings (file 1-47-3510-12-7).

FINGOLIMOD – Multiple sclerosis treatment – Heart rhythm disorders. (EMA, European Union, April 20, 2012)

After reviewing the safety of fingolimod, the European Medicines Agency (EMA) recommends not indicating fingolimod for patients with a history of heart and/or

cerebrovascular conditions or who take heart-rate-lowering drugs. Due to the possibility of occurrence of heart rhythm disorders, fingolimod should not be used in patients with a second degree or high grade atrioventricular block, sinus node disease or QT prolongation.

Concomitant use of fingolimod with group IA, group III anti-rhythmic, beta-blocking and calcium-blocking agents is not recommended, given the few data available about their interaction and the possibility of additive effects in the heart.

In such patients, treatment should be indicated only if the expected benefits outweigh potential risks. Patients receiving the first dose should be monitored for heart rate at least for 6 hours after administration.

Patients with lowered basal heart rate, bradycardia, atrioventricular block or QT interval prolongation should be monitored for at least two hours and until resolution.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/04/news_detail_001498.jsp&mid=WC0b01ac058004d5c1&jsenabled=true

Readers are reminded that fingolimod is in a Risk Management Plan which includes heart monitoring hours after the first dose administration. ANMAT recommends taking the above mentioned precautions.

INTERNATIONAL NEWS OF POST-MARKETING STUDIES

BIPHOSPHONATES –Osteoporosis treatment – Risk of uveitis and scleritis. Mahyar Etminan et al. Inflammatory ocular adverse events with the use of oral biphosphonates: a retrospective cohort study. Canadian Medical Association Journal. February 4, 2012. Published on-line.

According to a retrospective cohort study, patients taking oral biphosphonates for the first time may be at a higher risk for developing uveitis and scleritis. The incidence rate for the 10.827 first-time users of biophosphonates amounted to 29/10.000 person/years for uveitis and 63/10.000 for scleritis. For nonusers the relative risk for uveitis among first-time users was 1.15 (CI 95%: 1.25-1.68) and for sclerosis it was 1.51 (CI 95% 1.34-1.68).

The statistical analysis was adjusted for age, sex, history of ankilosing spondilitis, diabetes, inflammatory bowel syndrome, lupus, multiple sclerosis, psoriasis, rheumatoid arthritis and sarcoidosis. Also, an adjustment was made for sulpha-containing medicines as they showed an increased risk for developing inflammatory eye disease. However, being a retrospective study, it was constrained by certain factors such as incomplete medical records.

http://www.cmaj.ca/content/early/2012/04/02/cmaj.111752.full.pdf

From 2004 to 2012, four cases of biphosphonate-related eye adverse events were reported: one case of blepharitis with alendronate; one case of dry eye; one case of uveitis and one case of eye ulcer with ibandronate. ANMAT recommends health professionals that the use of biphosphanates be investigated in cases of patients developing scleritis or uveitis.

FLUOROQUINOLONES - Antibiotics - Retinal detachment.
Mahyar Etminan et al. Oral Fluoroquinolones and the Risk of Retinal Detachment. Journal of the American Medical Association. 2012; 307(13): 1414-1419.

According to a retrospective study, patients taking fluoroquinolones (e.g. ciprofloxacin, levofloxacin) may have an increased risk for retinal detachment.
Said antibiotics cause other eye adverse reactions such as blurred vision, keratitis and photophobia, among others. The medical records of patients who visited an ophthalmologist between January 2000 and December 2007 in British Columbia, Canada were reviewed. Out of all these patients, 4300 had a retinal detachment and 3.3% was being treated with quinolones at the time of such event, as compared to 0.6% who did not take these drugs.

http://jama.ama-assn.org/content/307/13/1414.short

Since 2004, the National Pharmacovigilance System has received one report of fluoroquinolone-related eye adverse event corresponding to norfloxacin-related vision impairment.

Within the limitations of the above mentioned study, an association between quinolones and retinal detachment was verified but no cause-effect relation was determined.

Readers are reminded that fluoroquinolones should be prescribed for the shortest possible time appropriate to each pathology. Dispensation of these and other antibiotics requires a medical prescription as they are to be sold under a filed prescription only. Until concluding results are obtained, the Pharmacovigilance Department will continue post-marketing monitoring of fluroquinolone-containing drug products. Adverse events should be reported to snfvg@anmat.gov.ar or by accessing http://www.anmat.gov.ar/farmacovigilancia/principal.asp.

SIGNAL JOURNAL, WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING. MARCH 2012.

EVEROLIMUS – Antineoplasic and immunosupressive drug – Serious gastrointestinal disorders.

The number of serious gastrointestinal events with everolimus amounted to 47. These cases were: gastrointestinal hemorrhage, ulcer (duodenal, gastric and peptic), hematemesis and melena. Concomitant drugs reported were sorafenib, oral anticoagulants and bevacizumab, all of them plausible for serious gastrointestinal disorders.

Despite it is difficult to determine a causal relation in many patients due to other risk factors and the use of concomitant drugs, and considering this is an increasingly used drug product, it is important to take this risk of everolimus into consideration only when it is associated with drugs such as soranefib or bevacizumab.

It is essential to continue vigilance over everolimus-associated toxicities. ANMAT reminds readers that everolimus is included in a Risk Management Plan and that to date, no serious gastrointestinal disorders associated to this drug product have been reported to the National Pharmacovigilance System.

ONDANSETRON – Antiemetic drug – Serotonin syndrome.

Many cases of serotonin syndrome associated with the use of ondansetron have been published. VigiBase contains nine cases associated with the use of ondansetron and five cases related to the use of antagonists 5-HT_3. In seven cases, patients were concomitantly taking other drugs such as antipsychotics and antidepressants that may also account for the disorder.

The cases published and the VigiBase reports indicate that ondansentron may contribute to the development of serotonin syndrome. The participation of ondansetron cannot be completely evaluated where there are alternative explanations but it cannot be ruled out as a contributor to the event. Furthermore, it should be noted that, many times, the serotonin syndrome is not recognized as such and therefore, cases are under reported.

Serotonin syndrome is a reaction that, many times, can be prevented and predicted. Signs and symptoms include altered mental status, autonomous nervous system hyper-reactivity and neuromuscular disorders.
Ondansetron should be considered as a possible adjuvant or contributor in the genesis of serotonin syndrome in predisposed patients such as those treated with psychotic drugs.

NATIONAL NEWS

Influenza vaccine – Vaccines approved by ANMAT.

Following is the listing of influenza vaccines authorized by ANMAT for 2012:

Name of the vaccine	Marketing authorization holder
Agrippal S1	Novartis Argentina
Agrippal S1 Junior	Novartis Argentina
Fluad	Novartis Argentina
Fluarix	Glaxosmithkline

Fluvirin	Novartis Argentina
Influvac	Abbott Laboratories Argentina
Istivac	Sanofi Pasteur
Istivac Junior	Sanofi Pasteur
Istivac ID	Sanofi Pasteur
Nilgrip	Instituto Biológico Argentino
Nilgrip Junior	Instituto Biológico Argentino
Vaxigrip	Sanofi Pasteur
Vaxigrip Junior	Sanofi Pasteur

It should be noted that the Ministry of Health Vaccinator´s Manual usually includes only the vaccines purchased by said ministry. Vaccines not included in the Vaccinator´s Manual but that are approved by ANMAT can be applied during the campaign as well.

http://www.anmat.gov.ar/Medicamentos/vacunas.asp