ANMAT
Administración Nacional de Medicamentos, Alimentos y Tecnología Médica

INTERNATIONAL AND NATIONAL NEWS ON DRUG PRODUCTS SAFETY - AUGUST 2012

INTERNATIONAL NEWS FROM DRUG REGULATORY AGENCIES

ONDANSETRON – Antiemetic drug – QT prolongation.
(ANSM, France, 08/02/2012)
(MHRA, United Kingdom, 08/02/2012)
(AEMPS, Spain, 08/10/2012)

According to the results of a study showing a dose–dependent QT interval prolongation associated with ondansetron, a 16mg single dose is recommended for treating chemotherapy-induced nausea and vomiting. Ondansetron administration should be avoided in patients with congenital prolonged QT and precaution should be taken in patients with electrolyte disorders, heart failure, bradiarrythmias and concomitant use of QT prolonging drugs. The regulatory agencies of France, United Kingdom and Spain are to update patient information leaflets based on this new safety information.

http://ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Ondansetron-Zophren-R-et-generiques-et-allongement-dose-dependant-de-l-intervalle-QT.-Nouvelle-restriction-posologique-concernant-l-utilisation-intraveineuse-IV-Lettre-aux-professionnels-de-sante

http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON178189

http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2012/NI-MUH_FV_14-2012.htm

The United States drug regulatory agency, FDA, has already informed this new safety update (see Pharmacovigilance news of July 2012).

One holder of an ondansetron-containing drug product marketing authorization has informed, through file 1-47-14283-12-1, that it will update the patient information leaflet. The remaining holders of ondansetron-containing products marketing authorizations will follow suit.

STRONTIUM RANELATE – Osteoporosis treatment – Risk of thrombo-embolism and hypersensitivity.
(TGA, Australia, 08/2012)

The Australian drug agency has informed it will update patient information leaflets of drug products containing strontium ranelate as an active pharmaceutical ingredient. This decision is based on a safety review conducted by the EMA (European Medicines Agency). The review was triggered by the publication of a study carried out in France, in which 199 reported adverse reactions were identified from January 2006 to March 2009. Around one half of those reports related to venous thromboembolism and, approximately, a fourth of them to skin reactions. Both risks are already known and described in the adverse reaction and

warning sections of patient information leaflets. The risk of thromboembolic events is increased in patients with a history of such events as well as in immobilized or elderly patients. The incidence rate of serious skin reactions is low.

http://www.tga.gov.au/hp/msu-2012-04.htm

Last March, both the EMA and the Spanish drug regulatory agency informed these risks. ANMAT opened file 1-47-5668-12-7 to request holders of marketing authorization of strontium ranelate-containing products to update the contraindications section of patient information leaflets.

CODEIN – Opioid analgesic – Risk of serious adverse reactions in children (FDA, USA, 08/15/2012)

The FDA is currently reviewing reports of children who developed serious adverse reactions or died after having used codein to relieve pain following and tonsillectomy and/or adenoidectomy for treating obstructive sleep apnea syndrome. Recently, three cases of pediatric deaths and one of potentially mortal respiratory depression were documented in medical literature. These children (aged two to five) had received a codein dose within the therapeutic range and showed evidence of a genetic mutation (CYP 2D6 ultra-rapid metabolizers) that converts codein to morphine faster, therefore, concentrating it to life-threatening levels.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm315627.htm

To date, the National Pharmacovigilance System has not received any report of codein-associated respiratory depression.

ANMAT recommends:

- **Using the lowest dose for the shortest possible time.**
- **Considering the indication of other analgesics as an alternative to codein for pain treatment in pediatric patients during the post-operative period of tonsillectomy/adenoidectomy caused by obstructive sleep apnea.**

POST-MARKETING STUDIES

Machan CM, Hrynchak PK, Irving EL. Age-related cataract is associated with type diabetes and statin use. *Optom Vis Sci* 2012; 89:1165-1171.

According to a recently published study, patients using statins have an increased risk of age-related cataracts. The biologic plausibility of these results lays on the fact that the crystalline membrane requires high levels of cholesterol for the appropriate development of epithelial and transparency cells. The study included 6,397 diabetic and non-diabetic patients. As researchers point out, diabetes is a risk factor for developing cataracts and, therefore, they evaluated the prevalence of cataracts in diabetic patients who take statins (n = 452) and the prevalence in those non-diabetic patients who take statins (n = 5884). The mean age of diabetic patients was 14 years older than those non-diabetic ones. The prevalence of statin use in patients older than 38 years old amounted to 56% for people with type 2 diabetes and to 16% for non-diabetics. The use of statins was associated with a significantly increased risk of developing age-related cataracts (Odds Ratio = 1,57; CI 95% = 1.15 to 2.13) and some subtypes of cataracts, including a 48% higher risk for nuclear sclerosis and a 48% increase in posterior sub-capsular cataract.

The lack of information about the statin doses used and treatment duration can be pointed out as study limitations. As is the case with other adverse reactions, it is necessary to know the interval between the treatment onset and the appearance of the event. However, given the biologic plausibility, the certainty of the relation between statins and cataracts cannot be ruled out. Further research remains necessary for a conclusive determination.

NATIONAL NEWS

DENOSUMAB – Osteoporosis treatment – Risk of severe symptomatic hypocalcemia.

The pharmaceutical company holding the marketing authorization of denosumab has reported denosumab-associated cases of severe symptomatic hypocalcemia, including fatal ones. The risk was identified following a recent review of post-marketing stage cases. Patient information leaflets and the Risk Management Plan will be updated to include the information about this new safety matter.