ANMAT
Administración Nacional de Medicamentos, Alimentos y Tecnología Médica

INTERNATIONAL AND NATIONAL NEWS ON DRUG PRODUCTS SAFETY - MAY 2012

INTERNATIONAL NEWS FROM REGULATORY AGENCIES

FINGOLIMOD – Treatment of multiple sclerosis – New recommendations after the first dose.
(Afssaps, France, May 3, 2012)
(FDA, USA, May 14, 2012)

Last April, the European Medicines Agency (EMA) established new recommendations for cardiovascular control at the beginning of Fingolimod treatment. The French drug regulatory agency and the FDA adopted said recommendations.

Fingolimod is not recommended for patients with:

- Second grade Mobitz II or a higher grade atrioventricular block and/or sinus node dysfunction.
- QT interval prolongation.
- History of symtomatic bradycardia, syncope, coronary disease, cerebrovascular disease, heart failure, non-controlled hypertension and severe sleep apnea.
- Concomitant use of antiarrhythmic drugs such as quinidine, amiodarone, beta blockers, heart rate-lowering calcium channel blockers and digoxin. In these patients, treatment with fingolimod should be considered only if benefits far outweigh risks.
- For all patients, follow-up after the first dose should include:
- A 12-lead ECG prior to administering the first dose and 6 hours afterwards.
- Blood pressure and heart rate measurement every hour, during the 6 hours subsequent to the first dose administration.

If after the first-6-hour period, heart rate becomes lower than its basal value, monitoring should be extended for at least two hours or until heart rate increases.

Monitoring should be extended for over two hours and until complete resolution in the following cases:

- Atrioventricular block
- Heart rate below 45 beats per minute
- QT interval longer than 500 ms

http://www.ansm.sante.fr/Infos-de-securite/Lettres-aux-professionnels-de-sante/Surveillance-cardio-vasculaire-lors-de-l-instauration-du-traitement-par-GILENYA-fingolimod-Information-de-pharmacovigilance-Lettre-aux-professionnels-de-sante

http://www.fda.gov/Drugs/DrugSafety/ucm303192.htm

Readers are hereby reminded that this drug product is included in a Risk Management Plan (RMP). This Administration is currently assessing a change in the RMP to include the new recommendations above.

ESCITALOPRAM – Anti-depressant – QT prolongation.
(Health Canada, Canada, May 7,2012)

During 2011, the United States, Spain and United Kingdom drug regulatory agencies warned about the association of QT prolongation and treatment with escitalopram. In this regard, Canada agency will update the information for patients (labels) of escitalopram-containing drug products. This risk is dose-related and, therefore, new information for patients (labels) will also include dosing information. Recommendations include:

- Not using escitalopram in patients with underlying heart conditions such as congenital Long QT syndrome or QT interval prolongation related to other causes.
- Not prescribing escitalopram in patients who concomitantly use QT interval prolonging-drugs.

- Using a 10 mg maximum dose in patients older than 65 years and/or with liver failure and/or who concomitantly take cytochrome P450 inhibitors, as in such cases escitalopram blood level may be increased.
- Using a 20 mg maximum dose in most of all other patients.

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2012/2012_63-eng.php

Since 2004, the National Pharmacovigilance System has not been reported on escitalopram-associated QT prolongation.
This Agency recommends:

- **Not using escitalopram in patients with underlying heart conditions that may prolong the QT or concomitantly with other QT-prolonging drugs.**
- **Not administering more than 10 mg/day of escitalopram to patients over 65 years old with liver failure or who concomitantly take cytochrome P450 inhibitors.**
- **Monitoring electrolytes in blood such as potassium, magnesium and calcium in those patients who concomitantly take drugs that could cause electrolyte disturbances, since in such case, escitalopram-caused cardiac toxicity may be increased.**

Readers are hereby reminded that in December 2011, this agency opened file 1-47-16396-11-3 to request holders of marketing authorizations of escitalopram-containing drug products to update patient information leaflets to include the information above.

LENALIDOMIDE – Treatment of multiple myeloma – Risk for second neoplasias.
(FDA, USA, May 07, 2012)

In August 2011, the FDA notified the public of an increased risk of developing second neoplasias for lenalidome-treated patients with multiple myeloma. The United States drug regulatory agency finished the review of clinical trials conducted

on patients who were newly diagnosed with multiple myeloma or who relapsed and were taking lenalidome. The studies conducted showed that lenalidome-treated patients had an increased risk of developing second primary malignancies as compared to similar patients who received a placebo. Particularly, these studies showed an increase of acute myelogenous leukemia, myelodisplastic syndromes and Hodgkin lymphoma. The FDA is updating information for patients (labels) of lenalidome-containing drug products to include these new risks.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm250606.htm

In November 2011, this Agency requested holders of marketing authorizations of lenalidome-containing drug products to update patient information leaflets (file 1-47-21684-11-8). The risk of developing new malignancies associated with lenalidome has already been notified to the public through the pharmacovigilance news report of November 2011.

http://www.anmat.gov.ar/farmacovigilancia/Informe_noviembre_2011.pdf

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AZITHROMYCIN – Macrolide antibiotic - Cardiovascular risk.
(FDA, USA, May 17, 2012)

The FDA notified healthcare professionals that it is reviewing a study published in the New England Journal of Medicine, which reports a small increase in cardiovascular deaths and deaths from any other cause of patients treated with azithromycin for five days, as compared to patients treated with amoxicillin, ciprofloxacin or no antibiotic. The American drug agency will timely communicate its conclusions about cardiovascular risk and QT prolongation. Health professionals should take these potential risks into account when indicating azithromycin or any other macrolide antibiotic.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm304503.htm?source=govdelivery

http://www.nejm.org/doi/pdf/10.1056/NEJMoa1003833

From the macrolide antibiotic group, clarithromycin and erythromycin have already been associated with cardiovascular events such as QT prolongation. Within this group, clarithromycin was so far considered as the one with the lowest risk of causing said events.

A.N.M.A.T. recommends:

- Treatments with macrolide antibiotics, including azithromycin, should not be interrupted when they are required by the patient´s condition or when no better therapeutic option is available.
- Reporting all QT prolongation and cardiovascular mortality events during treatments with macrolide antibiotics to the National Pharmacovigilance System.

TACROLIMUS – Ointment dosage form – Risk-minimizing measures. (Affsaps, France May 21, 2012)

The French drug regulatory agency notified healthcare professionals some risk-minimizing measures during treatment with tacrolimus in ointment dosage form. The reason for this is that this active pharmaceutical ingredient, when administered topically, is associated with an increased risk of developing skin tumors, including lymphoma. Cutaneous administration of tacrolimus is indicated for treating moderate to severe atopic dermatitis that does not respond to conventional treatment like corticoids. This drug should not be used in children younger than two years old since the possible effect on the immune system of this population is unknown. It should not be applied to potentially malignant lesions, patients with congenital or acquired immunodeficiency and those under immunosuppressive treatment.

http://www.ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Protopic-tacrolimus-0-03-et-0-1-pommade-Recommandations-importantes-de-bon-usage-afin-de-minimiser-les-risques-Lettre-aux-professionnels-de-sante

A.N.M.A.T. recommends taking the above described precautions and using treatment with tacrolimus ointment for the shortest possible time.