ANMAT
Administración Nacional de Medicamentos, Alimentos y Tecnología Médica

INTERNATIONAL AND NATIONAL NEWS ON MEDICINES SAFETY

DECEMBER 2012

NEWS FROM INTERNATIONAL REGULATORY AGENCIES

VARENICLINE – Nicotine receptor partial agonist. Review of cardiovascular event risks.
(FDA, United States, December 12, 2012)

Last June, the US drug regulatory agency had warned about a possible increased cardiovascular risk in subjects with a history of coronary disease who use this drug for smoking cessation purposes.

(See: http://www.anmat.gov.ar/farmacovigilancia/Informe_primer_semestre_2011.pdf)

Later on, FDA requested the manufacturer to carry out a meta-analysis in order to evaluate the drug cardiovascular safety. The study compared a group of varenicline-treated patients with a placebo-control group. Increased cardiovascular events were observed in patients treated with the drug. However, the difference between both groups was not statistically significant.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm331626.htm?source=govdelivery

ANMAT recommends health care professionals evaluating the risk-benefit balance of indicating the use of varenicline in subjects with a pre-existent cardiovascular disease.

ANMAT Pharmacovigilance Department has received to date only one report of a cardiovascular event possibly associated to the use of varenicline.

The National Pharmacovigilance System will continue to conduct safety monitoring on this medicinal product.

DABIGATRAN (Pradaxa®) – Anticoagulant – Not to be used in patients with mechanical heart valves.
(FDA, United States, December 19, 2012)
(AEMPS, Spain, December 19, 2012)
(Health Canada, Canada, December 24, 2012)

US, Spain and Canada drug regulatory agencies have informed the results of a review that concludes not to use dabigatran in subjects with mechanical prosthetic heart valves.

In this regard, the clinical study “RE-ALIGN trial” was disrupted as patients with mechanical prosthetic valves presented with hemorrhagic and thrombo-embolism events more frequently than those treated with warfarin.

Likewise, a higher risk of bleeding was observed after valve surgery in the dabigatran-treated patients as compared with the group receiving warfarin.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm332949.htm?source=govdelivery

http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2012/NI-MUH_FV_17-2012-dabigatran.htm

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2012/2012_204-eng.php

http://clinicaltrials.gov/ct2/results?term=1160.113+&Search=Search

Holders of marketing authorizations of dabigatran-containing medicinal products are reminded about the importance of keeping updated patient information leaflets.

TELAPREVIR (Incivo®) – Antiviral for treating hepatitis C – Risk of serious skin reactions.
(FDA, United States, December 19, 2012)

US drug regulatory agency has informed through a safety communication about the risk of serious skin reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome, DRESS syndrome) occurred in subjects receiving telaprevir in combination with peginterferon alfa and rivabirin for hepatitis C treatment.

Cases of death have been reported of patients who continued the treatment with telaprevir after presenting with serious progressive skin rash associated to systemic symptoms.

http://www.fda.gov/Drugs/DrugSafety/ucm332731.htm

In Argentina, this active pharmaceutical ingredient is included in a Risk Management Plan.

Holders of marketing authorizations of telaprevir-containing products will be requested to update patient information leaflets.

ANMAT Pharmacovigilance Department has not received to date any report on adverse skin reactions in patients under a combination therapy with Incivo, peginterferon and rivabirin.

ANMAT recommends immediate disruption of the combination therapy with telaprevir, peginterferon and rivabirin in subjects presenting with skin rash with systemic symptoms or a serious and progressive skin rash.

NATIONAL NEWS

ADALIMUMAB (Humira®) – Tumor necrosis factor inhibitor. Risk of Merkel cell carcinoma and neuroendrocrine carcinoma and pyrexia.

By means of file 1-0047-18481-12-0, manufacturer Abbott Argentina has informed about the risk of Merkel cell carcinoma and pyrexia in subjects treated with Humira.

The above manufacturer informed it will update patient information leaflets to include this piece of safety information with the recommendation that all the patients, particularly those treated with immune-suppressive drugs for long periods or patients with psoriasis receiving PUVA should be checked for non-melanoma skin carcinoma before and during treatment with adalimumab.

Likewise, it was informed that based on post-marketing reports an increased risk of pyrexia was identified in patients treated with this drug, apparently not related to usual causes such as infection or malign processes.

Last year, the Pharmacovigilance Departament received two reports of skin malign neoplasies possibly associated to the use of adalimumab.

AGOMELATINE – Antidepressant – Request of patient information leaflets update.

By means of Files Nº 1-47-9219/10-8, 1-47-23510/12-0 and 1-47-18272/12-9, ANMAT Pharmacovigilance Department has requested holders of marketing authorizations of agomelatine-containing products to update the information in patient leaflets concerning the control of liver function parameters, due to the risk of hepatotoxicity in patients treated with this drug (see October Pharmacovigilance news).

Public is reminded that agomelatine is included in a Risk Management Plan.

LAPENAX (CLOZAPINE) – Manufacturer Novartis Argentina – Change in 25mg and 100mg tablets.

Manufacturer Novartis Argentina S.A. has requested ANMAT authorization to make changes in the tablets of its product Lapenax. The request was made through File 1-47-19634-08-4.

Changes are as follows:

Table 1. Comparison between previous and current characteristics of Lapenax tablets.

	Previous	**Current**
Characteristics	25mg x 100 tablets	25mg x 100 tablets
Aspect	Yellow, rounded, flat, beveled edges Side 1: score Side 2: SANDOZ triangle	Yellow, rounded tablets Side 1: “LO” Side 2: “SANDOZ”
Smell	From odorless to weak characteristic smell	From odorless to weak smell
Average weight	152mg - 168mg	90mg - 100mg

	Previous	**Current**
Characteristics	100mg x 100 tablets	100mg x 90 tablets
Aspect	Yellow, rounded, flat, beveled edges Side 1: score Side 2: SANDOZ triangle	Yellow, rounded, flat, beveled edges Side 1: “ZA” Side 2: “SANDOZ”
Average weight	214mg - 236mg	361mg – 399mg

As shown in the chart, even though the tablet weight was changed, the strength remained the same.

http://www.anmat.gov.ar/boletin_anmat/abril_2011/Dispo_2729-11.pdf

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VACCINES

VACCINE AGAINST MENINGITIS B – Europe drug regulatory agency recommends approving the first vaccine against meningitis B in Europe.
(EMA, European Union, November 16, 2012)

The EMA Committee for Medicinal Products for Human Use (CHMP) has recommended authorizing the marketing within the European Union of the first vaccine against the invasive infection caused by Neisseria meningitidis group B, to be used in children older than two months.

Most cases of meningitis and septicemia are caused by 13 serogroups, among which subtype B is the most prevalent in Europe.

Even when there are vaccines authorized to prevent infections caused by serotypes A, C, W135 and Y, to date there is no vaccine providing immunity against meningococcal disease caused by subtype B.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_001656.jsp&mid=WC0b01ac058004d5c1

In Argentina, the meningococcal disease is considered endemo-epidemic. It can be serious and life-threatening. The most prevalent serogroup is B, though W135 is on the high.

Currently, the indication of conjugated meningococcal vaccines for healthy children and adolescents is determined on an individual basis.

http://www.sap.org.ar/docs/publicaciones/ConsensoVacunas2011.pdf

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PNEUMOCOCCAL VACCINE
(EMA, European Union, November 15, 2012)

The EMA Committee for Medicinal Products for Human Use (CHMP) has recommended widening the indication for pneumococcal vaccine Prevenar 13 for the prevention of invasive pneumococcal disease, pneumonia and otitis media in children from 6 weeks to 17 years old.

In Argentina, ANMAT authorized the inclusion of this vaccine in the Register of Medicinal Products in March 2010. Likewise, this vaccine was added to the National Vaccination Schedule in January 2012. Currently, it is indicated for the prevention of invasive pneumococcal disease, pneumonia and acute otitis media caused by S. pneumonia of the serotypes contained in the vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) in infants and children from 6 weeks to 5 years and adults older than 50 years.

http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/001104/WC500134840.pdf

http://www.anmat.gov.ar/prospectos/WYETH/DISPO_0634-12_C55413.PDF

http://www.msal.gov.ar/images/stories/calendario-vacunacion/calendario_vacunacion_web_2012.jpg

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POST MARKETING STUDIES

DOMPERIDONE – Peripheral dopamine blocker – Risk of serious heart arrhythmias and sudden cardiac death.
(Australian Prescriber, Vol 3, 12/2012)

Recent epidemiologic studies show that the use of domperidone is associated to an increased risk of ventricular arrhythmias or sudden cardiac death, particularly, in patients treated with doses greater than 30 mg/day and in subjects older than 60 years of age.

http://www.australianprescriber.com/magazine/35/6/192/201

ANMAT recommends:

- **Using domperidone at the lowest possible effective doses**
- **Avoiding the use of doses greater than 30 mg/day**
- **Having special precaution with subjects older than 60 years old**
- **Not using domperidone jointly with ketoconazole, erythromicin or other potent CYP3A4 inhibitors that prolong QT, such as fluconazole, clarythromicin or amiodarone**
- **Using it with caution in patients with preexisting cardiovascular risk factors (those with QT prolongation, heart failure, electrolyte disturbances or receiving drugs that can increase plasma levels of domperidone such as ritonavir, nifedipine, verapamil, itraconazol, etc)**

The National Pharmacovigilance System has not received to date any report of heart arrhythmias or sudden cardiac death associated to the use of domperidone.

Holders of marketing authorizations of domperidone-containing medicinal products are reminded to keep updated patient information leaflets.