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WHO Vision for Medicines Safety
No country left behind: worldwide pharmacovigilance for safer medicines, safer patients

The aim of the Newsletter is to disseminate regulatory information on the safety of pharmaceutical products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Safety and Vigilance: Medicines,

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This Newsletter is also available at:
http://www.who.int/medicines

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from the WHO global database of individual case safety reports, VigiBase.

This newsletter includes a brief report on the 40th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

Contents

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Feature

Amoxicillin containing products

Risk of thrombocytopenia

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for amoxicillin preparations have been updated to include the risk of thrombocytopenia as a clinically significant adverse reaction.

Amoxicillin is an antibiotic used for the treatment of a number of bacterial infections.

A total of nine cases of thrombocytopenia associated with use of amoxicillin have been reported in Japan. Of these, a causal relationship could not be excluded in five cases.

Reference:
Revision of Precautions, MHLW/PMDA, 17 October 2017 *(www.pmda.go.jp/english/)*

Chlorhexidine containing products

Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for chlorhexidine containing products, including over the counter preparations (Hibitane®, Acesclean®, Despakowa® and others) have been updated to include the risk of anaphylaxis as a clinically significant adverse reaction.

Chlorhexidine is generally used for disinfection.

A total of 12 cases associated with shock or anaphylaxis have been reported in Japan. Of these, a causal relationship could not be excluded in four cases.

Reference:
Revision of Precautions, MHLW/PMDA, 17 October 2017 *(www.pmda.go.jp/english/)*

(See page 10 and WHO Pharmaceuticals Newsletters No.2, 2017: Rare but serious allergic reactions in the USA and No.3, 2016: Serious allergic reactions in Canada)

Clozapine

Amendments to the patient monitoring programme

Spain La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) has reduced restrictions made in the patient monitoring programme on clozapine. It is no longer a requirement to send results of blood and laboratory tests to the AEMPS when prescribing clozapine.

Clozapine is an antipsychotic used to treat symptoms of schizophrenia and psychotic disorders associated with Parkinson's disease, when standard treatments are not effective.

Regular blood and laboratory tests (weekly and monthly leukocyte counts) have shown to be effective in preventing the occurrence of agranulocytosis and possible complications. However, in order to reduce the burden associated with sending blood results, the monitoring programme has been simplified:

It is not mandatory for prescribing doctors to send results of blood tests to the AEMPS, however this does not exempt them from carrying out the tests and keeping records of results in accordance to the license authorization conditions.

- Doctors no longer need to deliver the patient's chart at the time of prescription and pharmacies do not need to request it from the patient in order to dispense.
- Medicines that contain clozapine continue to be classified as medically controlled and, therefore, subject to dispensing requirements.

It should be remembered that blood and laboratory tests should be continued in patients undergoing treatment and prescription and dispensing conditions have not been modified.

Reference:
Información dirigida a profesionales sanitarios, AEMPS, 4 October 2017, Spain (*www.aemps.gob.es*)

(See WHO Pharmaceuticals Newsletter No.5, 2015: Modifications for monitoring neutropenia in USA)

Codeine-containing products

Contraindication in children and ultra-rapid metabolisers

Australia. The Therapeutic Goods Administration (TGA) has updated the product information documents for all prescription codeine preparations to include the restriction of use in children and ultra-rapid metabolisers. More specifically, codeine products should no longer be used in children under 12 years of age, or in children aged 12-18 years who have recently undergone surgery to remove their tonsils or adenoids. Codeine should also not be used by breastfeeding mothers or in patients known to be ultra-rapid metabolisers.

Most product information for over-the-counter codeine preparations now have warnings to not use them in children aged under 12 years.

From 1 February 2018, all "Pharmacy Medicine" and "Pharmacist Only Medicine" codeine-containing products will be rescheduled to "Prescription Only Medicine".

Reference:
Medicines Safety Update, TGA, Vol. 8, No. 5, November 2017 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.4, No.3, No.2 and No.1, 2017, No.5 and No.1 in 2016, No.6, No.5, No.4 and No.3 in 2015 for related information)

Daclizumab

Risk of serious liver damage

Europe. The European Medicines Agency's (EMA) has concluded that further restrictions on the use of the daclizumab (Zinbryta®) are necessary following a review of the medicine's effects on the liver.

Daclizumab is a medicine used to treat certain patients with relapsing forms of multiple sclerosis.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) review found that unpredictable and potentially fatal immune-mediated liver injury can occur during treatment with daclizumab and for up to six months after stopping treatment.

In order to reduce the risks, doctors should now only prescribe daclizumab for relapsing forms of multiple sclerosis in patients who have had an inadequate response to at least two disease modifying therapies (DMTs) and cannot be treated with other DMTs.

In addition, doctors should monitor patients' liver function (ALT, AST and bilirubin) at least once a month as closely as possible before each treatment and continue monitoring them for up to six months after treatments have stopped.

If the patient does not comply with monitoring requirements or the response to treatment is inadequate, doctors should consider stopping treatment.

It is recommended that the doctor should stop treatment if a patient has liver enzyme levels over three times the normal limit and refer patients with signs and symptoms of liver damage to a liver specialist.

Patients who test positive for hepatitis B or C infection should also be referred to a specialist.

Daclizumab must not be used in patients with pre-existing liver disease and should not be started in new patients with over two times the normal range of liver enzymes. It is recommended that doctors do not use daclizumab in patients with other autoimmune conditions.

The PRAC is also recommending that, in addition to the current educational materials, patients and health-care professionals in the EU should be given an acknowledgment form. The form will be used to confirm that doctors have discussed the risks with their patients and that the patients understand the importance of monitoring and checking for signs of liver damage.

Reference:
News and press releases, EMA, 27 October and 10 November 2017 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletter No.4, 2017: Provisional restrictions for use in EU)

DPP-4 inhibitors

Risk of arthralgia

India. The Pharmacovigilance Program of India, Indian Pharmacopeia Commission (PvPI, IPC) has made recommendations to the Central Drugs Standard Control Organisation (CDSCO) about revising the drug safety labels for DPP-4 inhibitors to include arthralgia as a potential adverse drug reaction.

DPP-4 inhibitors are used for the treatment of type 2 diabetes mellitus.

Between July 2011 and August 2017, PvPI received 96 reports of arthralgia with DPP-4 inhibitors use. The cases were reviewed by Signal Review Panel (SRP)-PvPI, IPC who concluded that there was a strong causal relationship between DPP-4 inhibitors and arthralgia.

Reference:
Based on the communication from IPC, NCC-PvPI, India, November 2017 (*www.ipc.gov.in*)

(See WHO Pharmaceuticals Newsletters No.3, 2017, No.6, 2015 and No.5, 2015 for related information)

Fingolimod

Contraindicated in patients with underlying cardiac pathology and risks of skin neoplasms

Spain After a periodic evaluation of safety data for fingolimod (Gilenya®), the AEMPS has recommended that health-care professionals should not use fingolimod in patients with underlying cardiac conditions.

Gilenya® is the only medication with fingolimod currently authorized in Spain. It is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (MS)).

During a periodic safety evaluation of fingolimod, an outstanding number of cases of polymorphic ventricular arrhythmias were detected after the administration of fingolimod.

Ventricular fibrillation and sudden death were among the cases described. In the deceased patients it was observed that there was a personal history of cardiac pathology.

Based on the evaluation, a number of risk minimization measures have been issued and this includes contraindication of use in patients with underlying cardiac conditions.

The AEMPS has also recommended that patients using fingolimod should be monitored for the appearance of skin lesions. Skin evaluations should be carried out at the beginning of the treatment and every 6-12 months afterwards.

The AEMPS has stated that cases of basal cell carcinoma as well as other skin neoplasms have been reported, including malignant melanoma, squamous cell carcinoma, Merckel cell carcinoma and Kaposi's sarcoma.

Reference:
Información dirigida a profesionales sanitarios, AEMPS, 6 November 2017, Spain (*www.aemps.gob.es*)

(See WHO Pharmaceuticals Newsletters No.1, 2016: Recommendations to minimise progressive multifocal leukoencephalopathy (PML) and skin cancer and No.5, 2015: Risk of progressive multifocal leukoencephalopathy in USA and Japan.)

Fluconazole

Risk of hyperpigmentation

India. The PvPI, IPC has made recommendations to the CDSCO about revising the drug safety label for fluconazole, to include hyperpigmentation as a potential adverse drug reaction.

Fluconazole is used for treatment of systemic mycosis and for prophylaxis of cryptococcal meningitis, oesophageal and oropharyngeal candidiasis, vaginal candidiasis and systemic candidiasis.

Between July 2011 and August 2017, PvPI received 12 reports of hyperpigmentation with fluconazole use. The cases were reviewed by SRP-PvPI, IPC who concluded that there was a strong causal relationship between fluconazole and hyperpigmentation in these cases.

Reference:
Based on the communication from IPC, NCC-PvPI, India, November 2017 (*www.ipc.gov.in*)

Fluconazole (non-prescription)

Potential risks to pregnancy outcomes

Canada. Health Canada has recommended that the product safety information for all non-prescription fluconazole products should be updated to include the potential risk of pregnancy loss and birth defects and state that these products are not recommended for use by women who are trying to become pregnant.

Non-prescription (oral, 150 mg) fluconazole products are authorized to treat vaginal yeast infections.

Health Canada reviewed the potential risk of unwanted effects in pregnancy, including pregnancy loss (i.e., miscarriage or stillbirth) or birth defects (i.e., major congenital malformations) with non-prescription fluconazole use, in part because a recently published study suggested that such a risk may exist.

At the time of the review, Health Canada had received one Canadian report and three international reports of miscarriages that were possibly related to non-prescription fluconazole use. Five international cases were identified in the information received from the manufacturers describing birth defects that were possibly associated with non-prescription fluconazole use; however there was not enough information in any of these reports to conclude a causal relationship.

A search in the WHO global database of Individual Case Safety Reports (ICSRs), VigiBase, found 360 cases of pregnancy loss or birth defects reported in patients treated with fluconazole. There was not enough information in these reports to conclude that fluconazole caused these outcomes or to determine whether the women were taking low dose fluconazole (150 mg or less) or higher doses. Higher dose fluconazole products, available by prescription only, are known to have pregnancy-related risks and these are communicated in the product safety information.

In the pregnancy registry study that suggested a link between fluconazole use and unwanted effects in pregnancy, there was not enough information to conclude whether or not the fluconazole product itself was the cause.

Health Canada's review found that a link between the use of non-prescription fluconazole and the risk of unwanted effects in pregnancy cannot be made at this time based on the currently available information.

The manufacturers have voluntarily updated the product safety information in prescription only products. Health Canada has recommended that the product information for all other non-prescription fluconazole products should be updated in the same way.

Women continue to be advised to avoid use of non-prescription fluconazole products while pregnant.

Reference:
Summary Safety Review, Health Canada, 9 November 2017 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.3, 2017: Reminder not to use during pregnancy in Ireland and Caution in use during pregnancy in Malaysia and No.3, 2016: Risk of miscarriage in pregnancy: under investigation in the USA)

Green tea extract-containing natural health products

Potential risk of liver injury

Canada. Health Canada has decided to strengthen the cautionary risk statement in the monograph for green tea extracts to include the advice

on the potential risk of liver injury.
Green tea extract-containing natural health products are used to help manage weight loss (along with diet and exercise) and as a source of antioxidants for the maintenance of good health.

Health Canada reviewed the potential risk of liver injury associated with green tea extract because of ongoing reports of serious liver injuries worldwide, including a recent report in Canada.

Health Canada's review concluded that there may be a link between the use of green tea extract and the risk of rare and unpredictable liver injury. While this risk is already identified in Health Canada's green tea extract's monograph, warnings will be strengthened.

The safety review also recommended that green tea extract products should be used by adults only.

Reference:
Summary Safety Review, Health Canada, 15 November 2017 (*www.hc-sc.gc.ca*)

Ibrutinib

Risk of ventricular tachyarrhythmia, hepatitis B reactivation and infection

Australia. The TGA has updated the product information for ibrutinib

trial data, 11 cases of ventricular tachycardia/ventricular fibrillation and six additional cases of sudden cardiac death in patients exposed to ibrutinib were identified. In 12 of these 17 cases, the events occurred without any evidence of prior cardiac history.

There were 52 cases of ventricular tachyarrhythmias reported in post-marketing settings.

A cumulative review of data from clinical trials and post-marketing cases identified eight reports of hepatitis B reactivation in ibrutinib-treated patients and causality of ibrutinib was considered to be probable or possible.

Infections (including sepsis, neutropenic sepsis, bacterial, viral or fungal infections) have been observed in patients treated with ibrutinib. Some of these infections resulted in hospitalisation and, in some cases, death.

Ibrutinib continues to have a favourable risk-benefit profile for treating patients with indications specified in the Australian product information.

Reference:
Medicines Safety Update, TGA, Vol. 8, No. 5, November 2017 (*www.tga.gov.au*)

Levetiracetam

reported in Japan. Of these, a causal relationship could not be excluded in two cases.

Reference:
Revision of Precautions, MHLW/PMDA, 17 October 2017 *(www.pmda.go.jp/english/)*

Linagliptin

Risk of interstitial pneumonia

Japan. The MHLW and the PMDA have announced that the package insert for linagliptin (Trazenta®) has been updated to include the risk of interstitial pneumonia as a clinically significant adverse reaction.

Linagliptin is a medicine used for type-2 diabetes mellitus.

A total of 20 cases associated with interstitial pneumonia have been reported in Japan. Of these, a causal relationship could not be excluded in four cases.

Reference:
Revision of Precautions, MHLW/PMDA, 17 October 2017 *(www.pmda.go.jp/english/)*

Moxifloxacin (oral dosage form)

Risk of rhabdomyolysis

Japan. The MHLW and the PMDA have announced that the