World Health Organization

WHO Pharmaceuticals NEWSLETTER

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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 information on the safety and efficacy 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:

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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 across the world. It also provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

A brief report from the Thirteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) is included as a feature.

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Regulatory Matters

Safety of Medicines

Alpha lipoic acid

Potential risk of low blood sugar (hypoglycaemic episodes)

Canada. Health Canada will consider updating the labelling standard for alpha lipoic acid to include advice on management of hypoglycaemic episodes. This follows conclusions from a safety review of case reports and publications in the scientific literature that indicate a risk of developing insulin autoimmune syndrome (IAS) with use of alpha lipoic acid (medicinal ingredient in natural health products).

Alpha lipoic acid is used as an antioxidant to help promote the breakdown of glucose, and as a preservative in some natural health products.

At the time of the review, there were no reports of hypoglycaemic episodes reported with the use of alpha lipoic acid that originated from Canada. However, there were several published international case reports of hypoglycaemic episodes in individuals with IAS which may have been triggered by the use of oral products containing alpha lipoic acid. The cases of hypoglycaemia resolved once the alpha lipoic acid was stopped.

There is scientific evidence of a genetic predisposition for IAS and risk of developing hypoglycaemic episodes with the use of oral alpha lipoic acid. Most cases reported originated from Asia (where these genetic variations are more common), and recently cases originating in Europe have been reported.

Reference:
Summary Safety Review, Health Canada, 30 June 2016 *(www.hc-sc.gc.ca)*

Apixaban

Risk of hepatic function disorder

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for apixaban (Eliquis®) has been updated to include the risk of hepatic function disorder as a clinically significant adverse reaction.

Apixaban is used to reduce the risk of ischemic stroke and systemic embolism in people with non-valvular atrial fibrillation. It is also used for treatment and prophylaxis of relapse of venous thromboembolism (deep vein thrombosis and pulmonary embolism).

A total of 16 cases of hepatic function disorder with the use of apixaban have been reported in Japan. Of these, a causal relationship could not be excluded in five cases.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 5 July 2016 *(www.pmda.go.jp/english/)*

Benzoyl peroxide

Risk of wide-spread swelling

Japan. The MHLW and the PMDA have announced that the package inserts for benzoyl peroxide preparations (Bepio® and Duac combination gel®) have been updated to include the risk of wide-spread swelling as a precaution.

Benzoyl peroxide is indicated for acne vulgaris. It is available as a single agent or in combination with clindamycin (Duac combination gel®).

A total of seven cases of cutaneous symptoms with the use of benzoyl peroxide have been reported in Japan. Of these, a causal relationship could not be excluded in six cases.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reports on the cases of erythema and swelling spreading to the entire face and neck will be added as a precaution to the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 5 July 2016 *(www.pmda.go.jp/english/)*

Bisphosphonates

Risk of osteonecrosis of external auditory canal

Japan. The MHLW and the PMDA have announced that the package inserts for bisphosphonates (etidronate, pamidronate, alendronate, risedronate, zoledronic acid, minodronic acid and ibandronate) have been updated to include the risk of osteonecrosis of external auditory canal as an important precaution and a clinically significant adverse reaction.

Bisphosphonates are indicated for osteoporosis, Paget's disease of bone, or used for prevention of heterotopic ossification in the early or advanced stages.

Osteonecrosis of external auditory canal was added to the Summary of Product Characteristics for bisphosphonates in Europe. In addition, cases have been reported in people treated with bisphosphonates in Japan and in other countries.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA

concluded that revision of the package insert was necessary.

(See WHO Pharmaceuticals Newsletter No1, 2016: Risk of osteonecrosis of the external auditory canal in the United Kingdom)

Reference:
Revision of Precautions, MHLW/PMDA, 31 May 2016 *(www.pmda.go.jp/english/)*

Bromhexine-containing cough and cold medicines

Risk of allergy and skin reactions

Australia. The Therapeutic Goods Administration (TGA) has advised that product information for all bromhexine-products (including generics) should contain information on the small risk of severe allergic reactions and severe skin reactions. The current package insert for the brand, Bisolvon®, already includes a warning regarding anaphylactic reactions and skin reactions.

A number of over-the-counter cough and cold medicines contain bromhexine as a mucolytic.

As of 19 February 2016, 34 cases of hypersensitivity reactions, 10 cases of anaphylactic/anaphylactoid reactions, and five cases of severe cutaneous adverse reactions (SCARs) had been reported to the TGA.

A definite link to bromhexine in 29 of these cases could not be made because: they involved products with multiple active ingredients or excipients such as benzoates which can also cause hypersensitivity; or there were other confounding factors.

The TGA reviewed this issue following a review by Europe's Pharmacovigilance Risk Assessment Committee (PRAC) that confirmed the risk of severe allergic reactions and SCARs associated with bromhexine- and ambroxol-containing medicines. Subsequently, product information for these products was updated with warnings of these potential adverse events.

The TGA has found that similar warnings to those being implemented in Europe are appropriate for bromhexine-containing medicines marketed in Australia.

(See WHO Pharmaceuticals Newsletter No.2, 2015: Risk of allergy and skin reactions with the use of ambroxol and bromhexine expectorants in the EU)

Reference:
Medicines Safety Update, TGA, Vol. 7, No. 3, June 2016 *(www.tga.gov.au)*

Canagliflozin and dapagliflozin

Strengthened warnings for acute kidney injury

USA. The US Food and Drug Administration (FDA) has revised the product information for canagliflozin (Invokana® and Invokamet®) and dapagliflozin (Farxiga® and Xigduo XR®) to strengthen the existing warning about the risk of acute kidney injury and to include recommendations to minimize this risk.

Canagliflozin and dapagliflozin are prescription medicines used with diet and exercise to help lower blood sugar in adults with type 2 diabetes.

From March 2013, (when canagliflozin was approved), to October 2015, the FDA received 101 reports of acute kidney injury, some of which required hospitalization and dialysis, with canagliflozin or dapagliflozin use.

The FDA has recommended that health-care professionals should consider factors that may predispose individuals to acute kidney injury prior to starting them on canagliflozin or dapagliflozin. Kidney function should be assessed prior to starting canagliflozin or dapagliflozin and monitored periodically thereafter. If acute kidney injury occurs, the drug should be discontinued promptly and kidney impairment should be treated.

(See WHO Pharmaceuticals Newsletter No.6, 2015: Risk of acute kidney injury with SGLT2 inhibitors in Canada)

Reference:
Drug Safety Communication, US FDA, 14 June 2016 *(www.fda.gov)*

Carmustine (intracerebral implant)

Possible risk of air accumulation at the implant site

Japan. The MHLW and the PMDA have announced that the package insert for carmustine intracerebral implant (Gliadel®) has been updated to include the possible risk of air accumulation at the implant site as an important precaution.

Carmustine intracerebral implant is used for the treatment of malignant glioma.

A total of 17 cases of air accumulation at the implant site with the use of carmustine intracerebral implant have been reported in Japan, although a causal relationship with the product was not established in all cases.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 5 July 2016 *(www.pmda.go.jp/english/)*

Diclofenac

Risk of gastrointestinal stenosis and obstruction

Japan. The MHLW and the PMDA have announced that the package inserts for diclofenac preparations (Voltaren® and Rectos®) have been updated to include the risk of gastrointestinal stenosis and obstruction as clinically significant adverse reactions.

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) and used for relief of pain and anti-inflammation.

A total of five cases of gastrointestinal stenosis or obstruction associated with the use of diclofenac have been reported in Japan. Of these, a causal relationship could not be excluded in four cases (one case was for a condition not included in the approved dosage and administration). In addition, the company core datasheet (CCDS) has been updated.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 5 July 2016 *(www.pmda.go.jp/english/)*

Febuxostat

Possible risk of Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS)

Canada. Health Canada has announced that the prescribing information for febuxostat (Uloric®) has been updated to include the risk of Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS).

Febuxostat is used to lower blood uric acid levels in people with gout.

Health Canada conducted a safety review of available evidence and concluded that there is a possible link between DRESS and use of febuxostat.

At the time of this review, Health Canada had received one report of DRESS originating from Canada in a patient taking febuxostat and ten cases from the manufacturer. The World Health Organization (WHO) Global Individual Case Safety Reports (ICSR) database, VigiBase®) had received 13 international cases. Three additional cases of DRESS in association with febuxostat therapy were reported in the scientific literature, two of which were also reported by the manufacturer.

Health Canada has also published an article to raise awareness and encourage reporting by patients and health-care professionals.

Reference:
Summary Safety Review, Health Canada, 13 June 2016 *(www.hc-sc.gc.ca)*

Fingolimod

Potential lack of efficacy for Primary Progressive Multiple Sclerosis (PPMS)

Japan. The MHLW and the PMDA have announced that the package inserts for fingolimod preparations (Imusera® and Gilenya®) have been updated to include a cautionary note for the potential lack of efficacy when used for primary progressive multiple sclerosis (PPMS).

Fingolimod is used to prevent relapse and to delay the accumulation of physical disability in multiple sclerosis (MS). MS can be categorised as: Relapsing-remitting MS (RRMS); PPMS; and Secondary Progressive MS (SPMS).

After evaluating the manufacturing authorization application for fingolimod, the PMDA has concluded that fingolimod is anticipated to be efficacious for SPMS with relapse.

Results from a clinical trial (D2306 Study) that was completed in July 2015 indicated that fingolimod did not demonstrate efficacy for PPMS.

For the time being, the PMDA does not think it is necessary to exclude PPMS from the indications of fingolimod based on lack of efficacy in one clinical trial which was conducted outside Japan. However, it is considered appropriate to be included in the section of precaution for indication.

Reference:
Revision of Precautions, MHLW/PMDA, 5 July 2016 *(www.pmda.go.jp/english/)*

Hydroxyzine

Potential risk of abnormal heart rhythm

Canada. Health Canada has updated dosing information for hydroxyzine (Atarax® and generics) to include advice on duration of dosing and new maximum daily doses (100 mg in adults and children over 40 kg), due to the potential risk of abnormal heart rhythm.

Hydroxyzine is a first-generation antihistamine used for anxiety; pruritus; pre-surgical medication; nausea and vomiting.

Health Canada conducted a safety review and concluded that there is evidence that hydroxyzine may contribute, along with other risk factors, to changes in the electrical activity of the heart and adversely affect heart rhythm.

At the time of Health Canada's review, there were 35 Canadian and 26 international cases of QT interval prolongation or torsades de

pointes (QTP/TdP) associated with the use of hydroxyzine reported. In the majority of these cases, the patients had additional risk factors, for example; concomitant medication (known to be associated with QTP/TdP and /or interact with hydroxyzine); electrolyte imbalances; family history; and exposure to daily doses of hydroxyzine over 100 mg.

Of these reports, only three cases (all international) provided enough information for a more detailed medical review. Hydroxyzine was found to have had a "possible" or "probable" contribution to QTP/TdP. However all cases had at least one other risk factor that could have contributed to development of QTP/TdP.

In addition, a review of the literature identified a slight QT interval prolongation after a single 100 mg dose of hydroxyzine in a recent clinical study, and with even higher doses in older clinical studies.

Health Canada is working with the manufacturers of hydroxyzine to update the product information to reflect the risk of changes in heart rhythm, especially in patients with predisposed risk factors.

(See WHO Pharmaceuticals Newsletters No.5, 2015: Risk of prolonged QT interval and ventricular tachycardia in Japan and No.3, 2015: Risks of effects on heart rhythm in Europe and Risk of QT interval prolongation and

about the initiation of idelalisib (Zydelig®) in patients with previously untreated chronic lymphocytic leukaemia (CLL) whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation).

Idelalisib is used for the treatment of CLL in patients who have received previous treatment as well as in previously untreated patients who have certain genetic mutations in their cancer cells (17p deletion or TP53 mutation). It is used in combination with rituximab.

The EMA's PRAC has completed a review of idelalisib confirming that the benefits outweigh risks for the treatment of CLL and follicular lymphoma.

At the beginning of the review the PRAC had advised, as a precaution, not to start idelalisib in patients with previously untreated CLL whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation). The PRAC now advises that idelalisib can again be initiated in these patients provided they cannot take any alternative treatment and that the measures agreed to prevent infection are followed.

The review confirmed that there is a risk of serious infections with idelalisib, including *Pneumocystis jirovecii* pneumonia; the PRAC has proposed updated recommendations to manage

Interferon beta-1a

Potential risk of kidney damage (nephrotic syndrome)

Canada. Health Canada has requested that the prescribing information for interferon beta-1a (Avonex®) is updated to include the potential risk of nephrotic syndrome.

Interferon beta-1a is used to reduce damage to the central nervous system, and slow down the worsening of multiple sclerosis (MS).

Health Canada carried out a safety review to investigate the potential risk of nephrotic syndrome with the use of interferon beta-1a.

At the time of the review, there was only one Canadian case of nephrotic syndrome reported in a patient with MS using interferon beta-1a.

A search in the WHO Global ICSR database, VigiBase® found 10 cases of nephrotic syndrome reported in MS patients treated with interferon beta products.

In the scientific and medical literature, there were seven cases of nephrotic syndrome found with the use of interferon beta products.

In addition, the manufacturer shared a report from the Global Safety Database which contained nine cases of nephrotic syndrome with interferon beta-1a. Upon