World Health Organization

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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®.

This newsletter includes two feature articles describing: the 40th meeting of the WHO International Working Group for Drug Statistics Methodology and the 39th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

The Safety and Vigilance team in WHO wishes all its readers across the world a very healthy and prosperous year in 2017.

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Allopurinol

Risk of drug-induced hypersensitivity syndrome

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for allopurinol (Zyloric® and others) have been updated to include the risk of drug-induced hypersensitivity syndrome (DIHS) as a clinically significant adverse reaction. Information on cases of DIHS related type 1 diabetes mellitus (including fulminant type 1 diabetes mellitus) and ketoacidosis have also been included.

Allopurinol is used for the management of hyperuricaemia in patients with gout or in hypertensive patients with hyperuricaemia.

A total of two cases associated with type 1 diabetes mellitus related to DIHS have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:
Revision of Precautions, MHLW/PMDA, 22 November 2016 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.5, 2016: Serious cutaneous adverse reactions and the role of genotyping in Singapore)

Alogliptin containing products, teneligliptin and linagliptin

Risk of pemphigoid

Japan. The MHLW and the PMDA have announced that the package inserts for alogliptin containing products (Nesina®, Liovel® and Inisync®), teneligliptin (Tenelia®) and linagliptin (Tradjenta®) have been updated to include the risk of pemphigoid as a clinically significant adverse reaction.

These products are indicated for type 2 diabetes mellitus.

A total of seven pemphigoid cases associated with alogliptin containing products, 14 cases with teneligliptin and 15 cases with linagliptin have been reported in Japan. Of these, a causal relationship could not be excluded in two, seven and ten cases, respectively.

Reference:
Revision of Precautions, MHLW/PMDA, 22 November 2016 *(www.pmda.go.jp/english/)*

Daptomycin

Risk of acute generalized exanthematous pustulosis

Japan. The MHLW and the PMDA have announced that the package insert for daptomycin (Cubicin®) has been updated to include the risk of acute generalized exanthematous pustulosis as a clinically significant adverse reaction. In addition, the company core datasheet has been updated.

Daptomycin is an antibiotic used to treat systemic and life-threatening infections caused by gram-positive organisms.

A total of two cases associated with acute generalized exanthematous pustulosis have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:
Revision of Precautions, MHLW/PMDA, 18 October 2016 *(www.pmda.go.jp/english/)*

Direct-acting antivirals for hepatitis C

Risk of hepatitis B reactivation

USA. The US Food and Drug Administration (FDA) has requested that a boxed warning about the risk of hepatitis B virus (HBV) reactivation is added to the drug labels of direct-acting antivirals for hepatitis C (DDAs). This warning should also be included in the patient information leaflets or medication guides for these medicines.

DAAs are used to treat chronic hepatitis C virus (HCV) infection.

The FDA identified 24 cases of HBV reactivation from reports submitted to the FDA and from the published literature in HCV/HBV co-infected patients treated with DAAs from 22 November, 2013 to 18 July, 2016. Of the cases reported, two patients died and one required a liver transplant. HBV reactivation was not reported as an adverse event in the clinical trials submitted for the DAA approvals because patients with HBV co-infection were excluded from the trials.

Health-care professionals are recommended to screen all patients for evidence of current or prior HBV infection before starting treatment with DAAs, and to monitor patients using blood tests for HBV flare-ups or reactivation during treatment and post-treatment follow-up.

Reference:
Drug Safety Communication, US FDA, 4 October 2016 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletter No.3, 2016: Risk of reactivation of hepatitis B virus in Japan)

Famciclovir

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for famciclovir (Famvir®) has been updated to include the risk of shock and anaphylaxis as clinically significant adverse reactions.

Famciclovir is indicated for herpes simplex and herpes zoster.

A total of three cases associated with shock or anaphylaxis have been reported in Japan. Of these, a causal relationship could not be excluded in all cases. The company core datasheet has also been revised. In addition, cases associated with shock or anaphylaxis are also reported in other countries.

Reference:
Revision of Precautions, MHLW/PMDA, 22 November 2016 *(www.pmda.go.jp/english/)*

Formalin containing products

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package inserts for formalin containing products used in dentistry have been updated to include the risk of shock and anaphylaxis as clinically significant adverse reactions. The contraindication for patients with a history of hypersensitivity to the ingredients of these products has also been included.

Formalin containing products are used for disinfection of infected root canals in dentistry or sealing, pain relief, sedation and pulp capping in paediatric dentistry among others.

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

Reference:
Revision of Precautions, MHLW/PMDA, 22 November 2016 *(www.pmda.go.jp/english/)*

Golimmab and certolizumab pegol

Risk of inflammation of the liver

Canada. Health Canada has updated the Canadian product information for golimmab (Simponi®) and certolizumab pegol (Cimzia®) to include information on available evidence regarding the risk of inflammation of the liver.

Golimmab and certolizumab pegol are Tumour Necrosis Factor (TNF) alpha blockers used to treat inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and psoriasis.

Health Canada has reviewed the link between TNF alpha blockers and liver inflammation following publication of two serious cases in the scientific literature, in which patients were treated with the TNF alpha blockers, adalimumab (Humira®) and infliximab (Remicade®).

At the time of this review, five serious cases of liver inflammation were reported with certolizumab pegol, of which one case was reported in the Canada Vigilance database. There were no cases of liver inflammation reported with the use of golimmab.

Of these five cases reported with certolizumab pegol three cases were assessed to be potentially linked to certolizumab pegol. These three patients improved when they stopped using certolizumab pegol. For the remaining two cases, either there was insufficient information available to establish a link with certolizumab pegol use or there were other possible explanations for liver inflammation.

Health Canada's review found a possible link between the risk of liver inflammation and the use of TNF alpha blockers. The Canadian product information for adalimumab, infliximab and etanercept (Enbrel®) already states liver inflammation as a very rare event that may lead to liver failure, but not for golimmab and certolizumab pegol.

Reference:
Summary Safety Review, Health Canada, 25 October 2016 *(www.hc-sc.gc.ca)*

HMG-CoA reductase inhibitors

Risk of immune-mediated necrotizing myopathy

Japan. The MHLW and the PMDA have announced that the package inserts for HMG-CoA reductase inhibitors (fluvastatin, pravastatin, simvastatin, atorvastatin, pitavastatin, rosuvastatin) and their combination preparations have been updated to include the risk of immune-mediated necrotizing myopathy as a clinically significant adverse reaction.

HMG-CoA reductase inhibitors are indicated for hyperlipidaemia and familial hypercholesterolaemia.

A total of three cases associated with immune-mediated necrotizing myopathy have been reported in Japan. Of these, a causal relationship could not be

excluded in two cases. The MHLW/PMDA have stated that cases of immune-mediated necrotizing myopathy have also been reported overseas.

Reference:
Revision of Precautions, MHLW/PMDA, 18 October 2016 *(www.pmda.go.jp/english/)*

Interferon beta products

Risk of pulmonary arterial hypertension

Canada. Health Canada has updated the Canadian product safety information for interferon beta products (type 1a (Avonex® and Rebif®) and type 1b (Betaseron® and Extavia®)) to include the risk of pulmonary arterial hypertension.

Interferon beta products are used to treat some forms of multiple sclerosis, a disease of the central nervous system.

Health Canada reviewed a possible link between the use of interferon beta products for treating multiple sclerosis and pulmonary arterial hypertension.

At the time of the review, there were two Canadian cases of pulmonary arterial hypertension that were possibly related to interferon beta use, and in both cases, the patients improved after treating the pulmonary arterial hypertension and stopping interferon beta use.

Worldwide, there were 136 case reports of pulmonary arterial hypertension in patients who were using interferon beta (which includes the two Canadian cases). In 14 cases, the pulmonary arterial hypertension may have been related to interferon beta use. In the remaining cases, the information available was too limited to make any conclusions.

Health Canada's safety review concluded that there was a possible link between the use of interferon beta products for multiple sclerosis and the risk of developing pulmonary arterial hypertension.

Reference:
Summary Safety Review, Health Canada, 2 November 2016 *(www.hc-sc.gc.ca)*

Levetiracetam and methotrexate

Drug-drug interaction

Canada. Health Canada has recommended that the product information for levetiracetam and methotrexate products is updated to provide information about drug-drug interaction, which could lead to greater amounts of methotrexate in the blood. Product labelling now recommends that blood methotrexate and levetiracetam levels should be carefully monitored in patients treated with the two drugs at the same time.

Levetiracetam is used to help epilepsy treatment be more effective. Methotrexate is used to treat cancer or to treat arthritis.

Health Canada carried out a safety review after learning that the European Medicines Agency (EMA) was looking into a potential interaction between levetiracetam and methotrexate.

At the time of the review, there were no reported cases in the Canada Vigilance Database of patients who had received levetiracetam and methotrexate at the same time.

The manufacturer of levetiracetam provided 13 international reports of a potential interaction between levetiracetam and methotrexate. The review of these reports was limited by many factors such as pre-existing diseases, other medications taken, and lack of laboratory data (e.g. blood levels of methotrexate). Of these 13 reports, five noted that patients who were taking both levetiracetam and methotrexate at the same time had greater amounts of methotrexate in their blood.

Health Canada's safety review concluded that there is a potentially greater risk of adverse effects when levetiracetam and methotrexate are taken together.

Reference:
Summary Safety Review, Health Canada, 24 October 2016 *(www.hc-sc.gc.ca)*

Lorazepam injection

Risks of amnesia and apnoea

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has announced that the package insert for lorazepam injection has been revised to include amnesia and apnoea as adverse reactions.

Lorazepam injection is used as pre-anaesthetic medication, or treatment of anxiety before examinations such as endoscopy, or in other anxiety disorders which require immediate drug action.

Through a review of adverse events reported in Korea Adverse Event Reporting System (KAERS) from January 1989 to June 2015, the MFDS and the Korea Institute of Drug Safety and Risk Management (KIDS) have identified a total of 11 cases associated with amnesia and three cases associated with apnoea.

This recommendation announced by the MFDS was based on a signal analysis

evaluation process using adverse event reports. Reports for lorazepam injections and amnesia/apnoea were identified to be statistically significant compared to all the other reports from other drugs.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, November 2016

(See WHO Pharmaceuticals Newsletter for a related case in No.2, 2016: Flunitrazepam - Precautionary measures for respiratory depression; and risk of apnoea, respiratory depression, and glossoptosis in Japan)

Nivolumab

Risk of excessive immunoreaction after discontinuation of treatment, immune thrombocytopenic purpura, myocarditis and rhabdomyolysis

Japan. The MHLW and the PMDA have announced that the package insert for nivolumab (Opdivo®) has been updated to include the risk of excessive immunoreaction after discontinuation of treatment as an important precaution; immune thrombocytopenic purpura, myocarditis and rhabdomyolysis as clinically significant adverse reactions.

Nivolumab is indicated for: radically unresectable malignant melanoma; unresectable, advanced, or

For immune thrombocytopenic purpura, a total of five cases have been reported in Japan. Of these, a causal relationship could not be excluded in three cases.

A total of six and four cases have been reported for myocarditis and rhabdomyolysis, respectively. Of these, a causal relationship could not be excluded in three and all cases, respectively. In addition, the company core datasheet has been updated.

Reference:
Revision of Precautions, MHLW/PMDA, 18 October 2016 *(www.pmda.go.jp/english/)*

Olanzapine

Risk of urinary retention

Canada. Health Canada has updated safety information for olanzapine to strengthen warnings of the potential risk of urinary retention. The update is consistent with the safety information provided for the other atypical antipsychotic products.

Olanzapine is used to treat mental disorders including schizophrenia, bipolar disorder and in some cases, depression.

Health Canada has carried out a safety review investigating the potential risk of urinary retention with the use of atypical antipsychotics.

between the atypical antipsychotic and urinary retention.

At the time of the review, there were 1254 international reports of urinary retention with the use of any of the atypical antipsychotics.

The risk of urinary retention is mentioned in the product safety information for most of the atypical antipsychotics. However, the wording used to explain the risk of urinary retention for the approved drug olanzapine was not consistent with the evidence reviewed.

Reference:
Summary Safety Review, Health Canada, 21 October 2016 *(www.hc-sc.gc.ca)*

Peramivir

Risk of acute renal failure

Japan. The MHLW and the PMDA have announced that the package insert for peramivir (Rapiacta®) has been updated to include the risk of acute renal failure as a clinically significant adverse reaction.

Peramivir is indicated for influenza A or B virus infection.

A total of seven cases associated with acute renal failure have been reported in Japan. Of these, a causal relationship could not be excluded in two cases.