World Health Organization

WHO Pharmaceuticals NEWSLETTER

2019 No.4

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 also includes update on pharmacovigilance strengthening activities in Ethiopia.

Contents

Suggested citation. WHO Pharmaceuticals Newsletter No.4, 2019: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Printed in Switzerland

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Alemtuzumab

Risk of serious cardiovascular and immune-mediated adverse reactions

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the use of alemtuzumab (Lemtrada®) will be restricted due to the risk of serious cardiovascular and immune-mediated adverse drug reactions. Strengthened requirements for monitoring alemtuzumab have been introduced in addition to an urgent safety review conducted by the EU.

Alemtuzumab is a monoclonal antibody indicated for the treatment of adults with relapsing-remitting multiple sclerosis.

Alemtuzumab should only be started in new patients with either: highly active relapsing-remitting multiple sclerosis if all other disease-modifying therapies are contraindicated; or relapsing-remitting multiple sclerosis that is highly active despite an adequate course of treatment with at least two other disease-modifying therapies. Patients already on alemtuzumab may continue treatment if beneficial and they have discussed the additional monitoring requirements with a health-care professional.

New monitoring requirements and precautions for use include: monitoring vital signs (e.g. blood pressure) before and periodically during alemtuzumab infusion, monitoring liver function tests and immediate evaluation of patients who develop early manifestations of pathologic immune activation.

Patients should be alerted of symptoms of: pulmonary haemorrhage, myocardial infarction, stroke, hepatic injury and haemophagocytic lymphohistiocytosis.

Reference:
Drug Safety Update, MHRA, 17 May 2019 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.3, 2019: Cardiovascular and immune-mediated adverse effects in Europe)

Avelumab

Risk of pancreatitis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for avelumab (Bavencio®) will be revised to include pancreatitis as an adverse drug reaction.

Avelumab is indicated for unresectable Merkel cell carcinoma.

Cases of pancreatitis have been reported in patients treated with avelumab overseas. Although no corresponding cases have been reported in Japan, the MHLW and the PMDA have concluded that the revision of the package insert was necessary based on their investigation of the currently available evidence and because there have been no findings to indicate ethnic differences in the pharmacokinetics and safety profile of the medicine between Japanese and overseas patients.

Reference:
Revision of Precautions, MHLW/PMDA, 4 June 2019 *(www.pmda.go.jp/english/)*

Baloxavir marboxil

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for baloxavir marboxil (Xofluza®) will be revised to include shock and anaphylaxis as adverse drug reactions.

Baloxavir marboxil is indicated for influenza A or B viral infections. Baloxavir marboxil inhibits the synthesis of viral RNAs.

A total of 42 cases involving shock or anaphylaxis have been reported in Japan during the previous three fiscal years. For 16 cases, a causal relationship between the drug and event could not be excluded. Additionally, one of the cases was fatal.

The MHLW and PMDA have concluded that revision of the package insert is necessary based on the results of their investigation of the currently available evidence and in consultation with expert advisors.

Reference:
Revision of Precautions, MHLW/PMDA, 4 June 2019 *(www.pmda.go.jp/english/)*

Cedar pollen extract powder, *dermatophagoides* extract bulk powder

Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the package inserts for cedar pollen extract (e.g. Cedartolen Japanese cedar pollen sublingual drop®) and *dermatophagoides* extract bulk powder (e.g. Actair house dust mite sublingual tablets®) will include anaphylaxis as an adverse drug reaction.

Cedar pollen extract is indicated for cedar pollinosis as desensitization therapy and *dermatophagoides* extract bulk powder is indicated for desensitization therapy against allergic rhinitis caused by mite antigens.

Patients should be alerted for the onset of anaphylaxis particularly when engaged in intense exercise, alcohol consumption or bathing. The reaction can take two or more

hours to occur following administration of the extracts.

Two cases of anaphylaxis have been reported in Japan during the previous three fiscal years. The reaction occurred after exercise or bathing within two or more hours after the cedar pollen extract was taken. Additionally, two cases of anaphylaxis have been reported with the use of *dermatophagoides* extract bulk powder. No patient mortalities have been reported.

Reference:
Revision of Precautions, MHLW/PMDA, 9 July 2019 *(www.pmda.go.jp/english/)*

Codeine, dihydrocodeine, tramadol

Contraindication in children: Risk of serious respiratory depression

Japan. The MHLW and the PMDA have announced that the package inserts for products containing codeine, dihydrocodeine or tramadol should be revised to include contraindications in children under 12 years of age (for all uses), and patients under 18 years of age when used for pain relief after tonsillectomy or adenoidectomy, due to the risk of serious respiratory depression.

Codeine, dihydrocodeine and tramadol are indicated to relieve coughs and pains.

Following the announcement of the US Food and Drug Administration (FDA) in 2017 of the contraindication of products containing codeine, dihydrocodeine or tramadol in children under 12 years, MHLW and PMDA have reviewed available safety information and concluded that the revision of package inserts is necessary.

In Japan there are four reports of morphine like toxic symptoms such as respiratory depression in patients using codeine, dihydrocodeine or tramadol. Mortality has not been reported.

Reference:
Revision of Precautions, MHLW/PMDA, 9 July 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.1, 2018: Limited use: Only for adults of 18 years of age and older in USA; No.6, 2017: Contraindication in children and ultra-rapid metabolisers in Australia; No.4, 2017: Cautions against use in children and teenagers under 18 years of age in Japan)

Epoprostenol

Risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced that the package insert for epoprostenol (Flolan®) should be revised to include thrombocytopenia as an adverse drug reaction.

Epoprostenol is indicated for pulmonary arterial hypertension.

A total of 18 cases of thrombocytopenia have been reported in Japan during the previous three fiscal years. For three cases, a causal relationship between the drug and event could not be excluded.

Patients should be monitored carefully and should have periodic laboratory tests. If any abnormalities are observed, dose reduction, discontinuation or other appropriate measures should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 9 July 2019 *(www.pmda.go.jp/english/)*

Febuxostat, topiroxostat

Potential risk of cardiovascular death

Japan. The MHLW and the PMDA have announced that the package inserts for febuxostat (Feburic®) and topiroxostat (Uriadec®) should be revised to warn about the potential risk of cardiovascular death in patients with cardiovascular disease.

Febuxostat and topiroxostat are indicated for gout or hyperuricemia.

The PMDA investigated studies conducted overseas. In the US, the CARES study showed a higher risk of cardiovascular death in the study group treated with febuxostat compared to the control group treated with allopurinol. The FDA restricted the use of febuxostat and revised the package insert in February 2019 to provide an alert on cardiovascular deaths.

The European Medicines Agency (EMA) required the marketing authorization holder of febuxostat to conduct a clinical study (FAST study) to assess the cardiovascular risks of febuxostat in patients with gout who had a cardiac disease The FAST study is ongoing.

In Japan, clinical trials do not show evidence of a higher incidence of cardiovascular events in the febuxostat study group compared to the control groups (placebo group or allopurinol group).

However, considering the evidence from studies conducted overseas and available evidence in the literature, PMDA has concluded that it is appropriate to add the CARES study results concerning cardiovascular death to package insert. Although no concerns were expressed about cardiovascular risks in a similar drug with a xanthine oxidase inhibitory effect, topiroxostat, it is

considered appropriate to add the same precautions to the package insert of topiroxostat.

Reference:
Revision of Precautions, MHLW/PMDA, 9 July 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.9, 2019: Increased risk of death in USA; No.6, 2017: Potential risk of heart-related death in USA; No.3, 2016: Risk of heart failure in Canada)

Fenspiride

Withdrawal due to the risk of heart rhythm problems

Europe. The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the marketing authorizations for cough medicines containing fenspiride (Elofen®, Epistat®, Eurefin®) should be revoked, due to the risk of heart rhythm problems.

Fenspiride is used to relieve cough resulting from lung diseases in adults and children of two years and older.

The PRAC considered all available evidence from cases of QT prolongation and torsades de pointes in patients using fenspiride. Heart rhythm problems can be serious, occur suddenly, and it is not always possible to identify patients at risk in advance. The use of fenspiride for treatment of cough is considered to be non-serious, and therefore the PRAC recommends that fenspiride should no longer be marketed.

Reference:
EMA, 17 May 2019 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletter No.3, 2019: Potential risk of problems with heart rhythm in Europe)

Gentian violet

Risk of cancer

Canada. Health Canada has announced that there is potential evidence of a link between the use of gentian violet and cancer.

Gentian violet is a non-prescription medicine used to treat cutaneous and mucocutaneous infections.

Following a review of the scientific literature and risk assessment on violet containing human therapeutic products, Health Canada concluded that the evidence from animal studies in the scientific literature suggests a potential link between gentian violet and cancer.

The assessments were triggered by a recommendation from the WHO's Codex Alimentarius Commission which advised regulatory authorities to prevent exposure to gentian violet in food due to a potential cause of cancer.

Health Canada notified the manufacturer of gentian violet of the assessment results. The manufacturer agreed to voluntarily discontinue marketing of their product in Canada and the health product drug licence for gentian violet has been cancelled.

Reference:
Summary Safety Review, Health Canada, 12 and 27 June 2019 *(www.hc-sc.gc.ca)*

Glucagon-like peptide-1 (GLP-1) receptor agonists

Risk of diabetic ketoacidosis

United Kingdom. The MHRA has requested that the Summaries of Product Characteristics and Patient Information Leaflets for Glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide, liraglutide and dulaglutide) are updated to include advice on reducing insulin dosage using a stepwise approach and monitoring of blood glucose to minimize the risk of diabetic ketoacidosis.

GLP-1 is indicated to treat adults with type-2 diabetes and are not substitutes for insulin.

There have been reports of diabetic ketoacidosis in patients with type-2 diabetes on a combination of a GLP-1 receptor agonist and insulin when the concomitant insulin is rapidly reduced.

An EU review concluded that the reported cases of diabetic ketoacidosis could be attributed to abrupt discontinuation or dose reduction of insulin while initiating GLP-1 receptor agonist therapy, resulting in poor glycaemic control.

Health-care professionals are advised that if the insulin dose is to be reduced, a stepwise approach is recommended. Also, they should monitor for signs and symptoms of diabetic ketoacidosis and risk factors with patients.

Reference:
Drug Safety Update, MHRA, 19 June 2019 *(www.gov.uk/mhra)*

Magnesium sulfate

Risk of skeletal adverse effects in neonates

United Kingdom. The MHRA has announced that the product information for products containing magnesium sulfate will be updated to warn of skeletal adverse effects observed with administration for more than five to seven days during pregnancy.

Magnesium sulfate is indicated for the prevention of further seizures associated with eclampsia in pregnancy and for the treatment of magnesium deficiency in hypomagnesemia.

In 2013, the US FDA issued a safety recommendation against the use of magnesium sulfate for more than five to seven days when used as a tocolytic (an indication not authorized in the UK). Such prolonged exposure may result in significantly higher cumulative doses than those encountered with use in the UK for eclampsia or foetal neuroprotection.

The MHRA is not aware of any reports in the UK of skeletal adverse effects or relevant biochemical effects in the neonate following use of magnesium sulfate but, considering that there is an increase in the usage in the UK, the decision to update product labels was made, based on the recommendations from the Paediatric Medicines Expert Advisory Group. The MHRA advises health-care professionals to consider monitoring neonates for abnormal calcium and magnesium levels and skeletal adverse effects if maternal treatment with magnesium sulfate is prolonged.

Reference:
Drug Safety Update, MHRA, 17 May 2019 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.6, 2015: Risk of hypermagnesaemia in Japan)

Metformin

Metformin is indicated to treat type-2 diabetes.

There was a concern that patients with renal impairment would be at a higher risk of lactic acidosis because the blood concentration of metformin increases due to a delay in its excretion. Therefore, it was contraindicated in patients with renal impairment including mild impairment.

In recent years, the FDA and the EMA have reviewed published papers and both organizations have concluded that metformin may be used in patients with mild to moderate renal impairment.

The PMDA considered the available information on pharmacokinetics, overseas published literature and guidelines, and concluded that metformin may be safely used in patients with moderate renal impairment if risks are minimized. Also, the package insert should include advise on low dose initiation of treatment, dose adjustments depending on the patient's condition, careful follow-up, and other required precautions in patients with renal impairment.

Reference:
Revision of Precautions, MHLW/PMDA, 18 June 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.3, 2016: Warnings for certain patients with reduced kidney function in USA)

treatment including malignant melanoma, unresectable, advanced or recurrent non-small cell lung cancer and relapsed or refractory classical Hodgkin lymphoma. They are classified as anti-programmed cell death protein-1 (PD-1) antibody medicines.

Cases of tuberculosis have been reported in patients treated with anti-PD-1 antibody medicines in Japan and overseas.

A total of 14 cases involving tuberculosis have been reported in Japan during the previous three fiscal years. For 10 cases, a causal relationship between the drug and the event could not be excluded.

The MHLW and PMDA have concluded that revision of the package insert is necessary based on the results of their investigation of the currently available evidence and in consultation with expert advisors.

Reference:
Revision of Precautions, MHLW/PMDA, 4 June 2019 *(www.pmda.go.jp/english/)*

2. Risk of enteritis

Japan. The MHLW and the PMDA have announced that the package inserts for nivolumab and pembrolizumab should be revised to include enteritis as an adverse drug reaction.

A total of 10 cases of enteritis, 35 cases of intestinal