World Health Organization

WHO Pharmaceuticals NEWSLETTER

2019
No. 2

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 a brief report on WHO missions to Lebanon and Ethiopia, for strengthening the national pharmacovigilance systems.

Contents

Suggested citation. WHO Pharmaceuticals Newsletter No.2, 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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Regulatory Matters

Safety of medicines

Signal

Baloxavir marboxil

Risk of bleeding

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for baloxavir marboxil (Xofluza®) should be revised to include bleeding as an adverse drug reaction and include a precaution on co-administration with warfarin.

Baloxavir marboxil is indicated for influenza A and B viral infections.

Patients and their families should be advised to contact their physician if bloody stool, epistaxis, haematuria or other forms of bleeding are observed, up to several days after administration of baloxavir marboxil.

A total of 25 cases of bleeding have been reported in patients treated with baloxavir marboxil in Japan during the previous three fiscal years. For 13 of the 25 cases a causal relationship with the product could not be excluded. Also, to date, three instances of patient mortality have been reported (a causal relationship with baloxavir marboxil could not be established).

MHLW and PMDA concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 1 March 2019 *(www.pmda.go.jp/english/)*

Carbimazole

Risk of acute pancreatitis

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for carbimazole is being updated to include the risk of acute pancreatitis.

Carbimazole is indicated for the treatment of hyperthyroidism, preparation for thyroidectomy, and pre-and post-radioiodine treatment.

In the UK, there have been no reports of acute pancreatitis associated with carbimazole treatment in the last 55 years. However, a small number of reports were received in other countries. The mechanism of action of recurrent acute pancreatitis after re-exposure to carbimazole suggests a possible immunological mechanism.

It is advised that carbimazole is discontinued immediately and switched to an alternative therapy in patients who develop acute pancreatitis during treatment.

Re-exposure to carbimazole should be avoided in patients who have previously experienced acute pancreatitis with carbimazole or its metabolite (thiamazole).

Reference:
Drug Safety Update, MHRA, 18 February 2019 *(www.gov.uk/mhra)*

Deferiprone

Potential risk of brain and nervous system disorders in children

Canada. Health Canada will ask manufacturers to update the safety information for deferiprone (Ferriprox®) to include information on reported cases of neurological disorders in children using recommended doses of deferiprone.

A warning of the risk of neurological disorders in children taking doses 2.5 times higher than the recommended dose already exists in the product information.

Deferiprone is indicated to remove excess iron accumulated in the body from blood transfusions in the treatment of thalassemia syndromes (genetic diseases of blood production).

Health Canada assessed the potential risk of brain and nervous system (neurological) disorders, such as difficulty walking or difficulty with the coordination of movement, in children treated with deferiprone at recommended doses. Health Canada concluded that there may be a link.

Health Canada encourages consumers and health-care professionals to report any adverse drug reactions related to the use of deferiprone.

Reference:
Summary Safety Review, Health Canada, 25 February 2019 *(www.hc-sc.gc.ca)*

Eliglustat

Contraindication: Co-administration of CYP2D6 and CYP3A inhibitors

Japan. The MHLW and the PMDA have announced that the package insert for eliglustat (Cerdelga®) should be revised to state that co-administration with CYP2D6 and CYP3A inhibitors is contraindicated.

Eliglustat is indicated to improve various symptoms of Gaucher disease (anaemia, thrombocytopenia, hepatosplenomegaly and bone disease). Eliglustat is metabolized mainly by CYP2D6 and partially by CYP3A4.

There have been no reports received for the co-administration of eliglustat with CYP2D6 and CYP3A inhibitors in Japan during the previous three fiscal years.

Based on results of an investigation and in consultation with expert advisors, MHLW and PMDA have also advised that the hepatic function of patients should be considered before

prescribing eliglustat. This has also been included in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 12 February 2019 *(www.pmda.go.jp/english/)*

Febuxostat

Increased risk of death

USA. The US Food and Drug Administration (FDA) has added a boxed warning for febuxostat (Uloric®) indicating an increased risk of death compared to its alternative, allopurinol.

This conclusion was based on an in-depth review of results from a safety clinical trial that found an increased risk of heart-related death and death from all causes with febuxostat.

Febuxostat is indicated to treat gout.

It is advised that the use of febuxostat should be reserved for patients who have failed or do not tolerate allopurinol. Patients should be informed about cardiovascular risks with febuxostat and should be advised to seek immediate medical attention if they experience symptoms such as: chest pain, shortness of breath, rapid or irregular heartbeat, numbness or weakness on one side of the body, dizziness, trouble talking, and sudden severe headache.

Reference:
Safety Alerts for Human Medical Products, US FDA, 21 February 2019 *(www.fda.gov)*

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

Fenspiride

Potential risk of problems with heart rhythm

Europe. The European Medicines Agency (EMA) has announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended an EU-wide suspension of preparations containing fenspiride (Epistat®, Eurefin®, Eurespal® and others) due to the potential risk of problems with heart rhythm.

Fenspiride is indicated to relieve cough caused by lung diseases in children and adults.

Cases of problems with heart rhythm had been reported in patients who had taken fenspiride in the past. An exploration of animal studies show that fenspiride has the potential to prolong the QT interval in humans.

PRAC will now examine all the available evidence and make recommendations on the action to be taken by marketing authorizations on fenspiride medicines across the EU.

Health-care professionals should advise their patients to stop taking preparations containing fenspiride.

Reference:
EMA, 15 February 2019 *(www.ema.europa.eu)*

Finasteride

Potential risk of suicidal ideation

Canada. Health Canada has requested that manufacturers update the product information for finasteride (Proscar® and Propecia®) to include the potential risk of suicidal thoughts and/or behaviour (suicidal ideation).

Finasteride is used to treat prostate gland enlargement (Proscar®), and male pattern hair loss (Propecia®).

A re-assessment of initial reviews in 2012 and 2014 found that the Canadian reporting rate for finasteride and suicide/self-injury-related events increased by 2.5 times between 2012 and 2016.

To date, Health Canada has received 26 reports of suicide and/or self-injury-related events reported in patients treated with finasteride. A search in the WHO global database of Individual Case Safety Reports, Vigibase (up to September 16, 2018), found 368 international reports. Health Canada has concluded that there may be a link between finasteride use and the risk of suicidal ideation.

Reference:
Summary Safety Review, Health Canada, 26 February 2019 *(www.hc-sc.gc.ca)*

(See WHO Pharmaceuticals Newsletter No.6, 2017: Risk of depression and suicidal thoughts in France; No.4, 2017: Rare reports of depression and suicidal thoughts in UK; No.1, 2016: Risk of suicidal thoughts and behaviour in Canada)

Fingolimod

Risk of worsening multiple sclerosis symptoms

Canada. Health Canada has updated the product information for fingolimod (Gilenya®) to include the risk of worsening multiple sclerosis (MS) symptoms following withdrawal (rebound effect).

Fingolimod is indicated to treat MS, and is specifically recommended for patients who have had a poor response to, or are unable to tolerate, one or more of the other therapies for MS.

Health Canada identified 29 international reports of severe worsening of MS disease progression after fingolimod withdrawal. Also, Health Canada reviewed information from the manufacturer and the scientific literature on the risk of a rebound effect following

withdrawal of treatment with fingolimod.

Health Canada's review concluded that there may be a link between the withdrawal of fingolimod and the worsening of MS symptoms (rebound effect).

Reference:
Summary Safety Review, Health Canada, 28 February 2019 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletter No.3, 2017: Potential rebound effect after stopping or switching therapy in UK)

Glecaprevir hydrate/pibrentasvir combination

Risk of hepatic impairment and jaundice

Japan. The MHLW and the PMDA have announced that the package insert for glecaprevir hydrate/pibrentasvir (Maviret Combination®) should be revised to include hepatic impairment and jaundice as adverse drug reactions.

Glecaprevir hydrate/pibrentasvir preparation is indicated to improve viraemia in patients with chronic hepatitis C or compensated cirrhosis C. Hepatic impairment accompanied with elevation of AST, ALT, or bilirubin levels and jaundice may occur.

Eleven cases involving hepatic impairment have been reported in patients treated with glecaprevir hydrate/pibrentasvir in Japan during the previous three fiscal years. For five of the 11 cases a causal relationship with the product could not be excluded. One of the 11 cases was fatal, a causal relationship with the product could not be established.

MHLW and PMDA concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 12 February 2019 *(www.pmda.go.jp/english/)*

Hydrochlorothiazide

Potential risk of non-melanoma skin cancer (NMSC)

1. Canada. Health Canada has requested manufacturers to update the product safety information for all hydrochlorothiazide-containing products to include the potential risk of non-melanoma skin cancer (NMSC).

Hydrochlorothiazide is used to treat high blood pressure and excess build-up of fluid.

Health Canada reviewed five studies that investigated the risk of NMSC with the use of hydrochlorothiazide alone or in combination with other medicines using data from thousands of patients. Health Canada's review suggests that there might be a risk of NMSC with prolonged use of hydrochlorothiazide.

Patients taking hydrochlorothiazide should be informed of potential risk factors (e.g. light-coloured skin, known personal or family history of skin cancer and ongoing immunosuppressive therapy) for NMSC and advised to regularly check their skin for new marks or growths as well as changes to existing ones.

Reference:
Summary Safety Review, Health Canada, 30 January 2019 *(www.hc-sc.gc.ca)*

2. Singapore. The Health Sciences Authority (HSA) has updated health-care professionals on the risk of NMSC with hydrochlorothiazide following the results from two recent pharmacoepidemiological studies using Danish registries.

The HSA has considered the EMA's conclusions, which suggest a biologically plausible mechanistic model supporting the increased risk of NMSC following higher cumulative doses of hydrochlorothiazide. HSA also considered Health Canada's conclusion that NMSC is a potential risk of prolonged hydrochlorothiazide treatment. However, uncertainty remains due to limitations in the studies.

HSA has not received any local reports of NMSC suspected to be associated with the use of hydrochlorothiazide.

While HSA's safety review is ongoing, health-care professionals should consider the findings from the two Danish pharmacoepidemiological studies when prescribing hydrochlorothiazide to their patients.

Reference:
Product Safety Alerts, HSA, 8 March 2019 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.1, 2019: Risk of non-melanoma skin cancer in Egypt; No. 6, 2018: Risk of non-melanoma skin cancer in UK)

Lithium

Risk of major congenital malformations

New Zealand. Medsafe has announced that it is working with manufacturers of lithium-containing medicines to provide up-to-date information on the risk of major congenital malformations with lithium use during pregnancy.

Lithium is a mood stabiliser used in the treatment of bipolar disorder.

Two recently published studies investigated the risk of congenital cardiac malformations. As a result, the risk was estimated at around 2-2.5% in both studies, while

the background rate of congenital cardiac malformations is around 1%.

Up to 1 November 2018, four cases of congenital malformations associated with the use of lithium in pregnancy had been reported to the Centre for Adverse Reaction Monitoring (CARM). Three of the cases described cardiac defects.

It is important for prescribers to discuss the benefits and risks of continuing lithium during pregnancy with women who have bipolar disorder and who are planning to, or have become pregnant.

Reference:
Prescriber Update, Vo. 40, No.1, Medsafe, March 2019 *(www.medsafe.govt.nz/)*

Macitentan

Potential risk of liver injury

Canada. Health Canada has requested that manufacturers update the safety information for macitentan (Opsumit®) to include the risk of liver injury.

Macitentan is used to treat certain types of pulmonary arterial hypertension (PAH).

Health Canada reviewed 15 Canadian reports of liver injury with macitentan. Of these reports, 14 were not found to be relevant to this review (e.g. duplicated, did not meet the definition), and it was

Reference:
Summary Safety Review, Health Canada, 1 March 2019 *(www.hc-sc.gc.ca)*

Nivolumab (genetical recombination)

Risk of serious blood disorder

Japan. The MHLW and the PMDA have announced that the package insert for nivolumab (Opdivo®) should be revised to include haemophagocytic syndrome, haemolytic anaemia and agranulocytosis as adverse drug reactions.

Nivolumab is indicated for various kinds of cancers (e.g. malignant melanoma, unresectable advanced or recurrent non-small cell lung cancer and relapsed or refractory classical Hodgkin lymphoma).

A total of 10 cases involving haemophagocytic syndrome have been reported in patients treated with nivolumab in Japan during the previous three fiscal years. For three of the 10 cases a causal relationship with the product could not be excluded. Likewise, a total of 15 cases involving haemolytic anaemia have been reported and a causal relationship could not be excluded. One fatal case has been reported. A total of 33 cases involving neutropenia

Opioids

Potential risk of opioid use disorder and related harms in children and adolescents

Canada. Health Canada has asked manufacturers to update the product safety information of opioid-containing cough and cold products to include limitations on the recommended age of use (adults only: 18 years of age and older).

Opioid-containing cough and cold products have been marketed in Canada since the 1950s. There are three prescription opioid drugs authorized to treat cough symptoms in adults and children in Canada: codeine, hydrocodone and normethadone. Low-dose codeine is also available without a prescription in most provinces. Currently, codeine products are not recommended for children under 12 years of age, and hydrocodone and normethadone products are not recommended for children under six years of age.

Health Canada reviewed the risk of opioid use disorder and related harms from these products and found limited evidence to link opioid-containing cough and cold products with opioid use disorders and related harms in children and adolescents.

Health Canada will also inform Canadians and health-care