World Health Organization

# WHO Pharmaceuticals NEWSLETTER

2018 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:*

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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 the latest news from the Smart Safety Surveillance (3S) project.

## Contents

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## Regulatory Matters



## Safety of medicines

## Signal



## Feature

## Amiodarone

### Risk of agranulocytosis and leukopenia

**Japan**. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for amiodarone (Ancaron®) should be revised to include agranulocytosis and leukopenia as adverse reactions.

Amiodarone is indicated for treatment of ventricular fibrillation, ventricular tachycardia, and heart failure when patients have not responded to other available antiarrhythmics or when alternative agents cannot be used.

A total of three cases associated with agranulocytosis and/or leukopenia were reported in Japan, and a causal relationship with amiodarone could not be excluded for one of these cases.

Based on the investigation of the evidence currently available, MHLW/PMDA have concluded that revision of the package insert was necessary.

***Reference:***
Revision of Precautions, MHLW/PMDA, 19 April 2018 *(www.pmda.go.jp/english/)*

## Benzocaine

### Risk of blood disorder in infants and children

**USA**. The US Food and Drug Administration (FDA) has announced that over the counter (OTC) oral medicinal products containing benzocaine (Anbesol®, Orabase®, Orajel®) should not be used to treat infants and children aged less than two years due to risk of blood disorders.

Benzocaine is a local anesthetic contained in some OTC products for the temporary relief of pain due to minor irritation, soreness, or injury of the mouth and throat.

Benzocaine can cause a condition in which the amount of oxygen carried through the blood is greatly reduced, called methemoglobinemia, which can be life-threatening and result in death.

In addition, manufacturers were requested to change the labels of benzocaine containing products to include: a warning about methemoglobinemia; contraindication in infants and children younger than two years; and revisions to the directions for parents and caregivers.

***Reference:***
Safety Alerts for Human Medical Products, US FDA, 23 May 2018 *(www.fda.gov)*

## Cladribine

### Risk of progressive multifocal leukoencephalopathy (PML)

**Japan**. MHLW and PMDA have announced that the package insert for cladribine (Leustatin®) should be revised to include progressive multifocal leukoencephalopathy (PML) as a clinically significant adverse reaction.

Cladribine is indicated for hairy cell leukemia and recurrent, relapsing, or refractory indolent B-cell non-Hodgkin's lymphoma including follicular lymphoma, and mantle cell lymphoma.

While there were no reports of PML in Japan however, there were cases of PML reported in patients exposed to cladribine overseas in the previous three fiscal years.

Based on the investigation of the evidence currently available, MHLW/PMDA have concluded that the revision of the package insert was necessary.

***Reference:***
Revision of Precautions, MHLW/PMDA, 19 April 2018 *(www.pmda.go.jp/english/)*

*(See WHO Pharmaceuticals Newsletters No.1, 2018: Risk of progressive multifocal encephalopathy (PML) in UK and Spain)*

## Clarithromycin

### Risk of arrhythmia, myocardial infarction and cardiovascular mortality

**Ireland.** The Health Products Regulatory Authority (HPRA) has announced that the product information for clarithromycin-containing medicinal products will be updated to reflect findings from observational studies which have identified a rare, short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with clarithromycin.

Clarithromycin is used to treat various bacterial infections.

It is known that clarithromycin has been associated with effects on QT prolongation and cardiac arrhythmias and the product information for clarithromycin provides guidance on use in patients at risk of ventricular arrhythmia and other cardiac conditions.

As part of a routine periodic assessment of clarithromycin-containing medicines by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA), cumulative evidence to date on cardiovascular safety of clarithromycin was reviewed. The PRAC noted that some observational studies have identified a rare, short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with clarithromycin. It is recommended that consideration of findings should be balanced with known treatment benefits when prescribing clarithromycin, particularly in patients with a high baseline cardiovascular risk.

***Reference:***
Drug Safety Newsletter, HPRA, June 2018 *(www.hpra.ie)*

*(See WHO Pharmaceuticals Newsletters No.2, 2018: Potential risk of heart problems or death in patients with heart disease in USA)*

## Daclizumab

### Potential risk of immune reactions

**Europe.** The European Medicines Agency (EMA) has announced that daclizumab (Zinbryta®) is no longer authorized for use in the EU and has been recalled from hospitals and pharmacies due to the risk of serious and potentially fatal immune reactions.

Daclizumab is indicated to treat relapsing forms of multiple sclerosis.

The EMA confirmed that daclizumab poses a risk of serious and potentially fatal immune reactions affecting the brain, liver and other organs. The EMA therefore confirmed its previous conclusion that the risk outweighs the benefit for patients with multiple sclerosis.

On 27 March 2018, the marketing authorisation was withdrawn.

***Reference:***
EMA, 18 May 2018
*(www.ema.europa.eu)*

*(See WHO Pharmaceuticals Newsletters No.2, 2018: Immediate suspension: risk of serious inflammatory brain disorders in Europe; No.6, 2017: Risk of serious liver damage in Europe; No.4, 2017: Provisional restrictions for use in Europe)*

## Darunavir

### Potential risk of treatment failure and maternal-to-child transmission of HIV-1

**United Kingdom.** The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for products containing darunavir (Prezista®, Rezolsta® and Symtuza®) will be updated to advise against the use of darunavir boosted with cobicistat during pregnancy due to risk of treatment failure and maternal-to-child transmission of HIV-1.

Darunavir is an antiretroviral medication used to treat and prevent HIV/AIDS. Cobicistat can be co-administered with darunavir as a booster to increase darunavir levels. They are available in combination in some products.

New pharmacokinetic data show mean exposure of darunavir boosted with cobicistat to be lower during the second and third trimesters of pregnancy. Low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child.

It has been advised that therapy with darunavir/cobicistat should not be initiated during pregnancy, and women who are pregnant and taking darunavir/cobicistat should be switched to an alternative regimen.

A letter has been sent to relevant health-care professionals to inform them of this information.

***Reference:***
Drug Safety Update, MHRA, 17 July 2018
*(www.gov.uk/mhra)*

## Dasatinib

### Risk of nephrotic syndrome

**The Netherlands.** The product information for dasatinib (Sprycel®) in all EU Member States has been updated to include the risk of nephrotic syndrome.

Dasatinib is used to treat chronic myeloid leukaemia and Philadelphia-chromosome positive acute lymphoblastic leukaemia.

The Netherlands Pharmacovigilance Centre Lareb has received one report of nephrotic syndrome associated with the use of dasatinib. This concerned a male aged between 11-20 years who developed nephrotic syndrome 27 days after starting dasatinib. The patient recovered one week after withdrawal of dasatinib and fluid intake restriction. Also the European pharmacovigilance database, EudraVigilance, contained seven strongly supportive cases concerning nephrotic syndrome. In addition, there were five cases reported in the literature and a causal relationship between dasatinib and nephrotic syndrome were found in these cases

***Reference:***
Based on the communication from the Netherlands Pharmacovigilance Centre Lareb, June 2018
*(www.lareb.nl/en/)*

## Denosumab

### 1. Risk of new primary malignancies

**United Kingdom.** The MHRA has announced that the product information for denosumab (Xgeva®) has been updated to include the risk of new primary malignancies.

Denosumab is indicated for the prevention of skeletal-related events, such as pathological fracture, and radiation to bone.

The decision to revise the product label for denosumab occurred following findings from a recent review conducted by the EU. An increased rate of new primary malignancies in patients given denosumab compared to those given zoledronic acid was reported when used for the prevention of skeletal-related events with advanced bone malignancies.

***Reference:***
Drug Safety Update, MHRA, 22 June 2018
*(www.gov.uk/mhra)*

### 2. Risk of hypercalcaemia

**United Kingdom.** The MHRA has announced that the Summary of Product Characteristics for denosumab has been updated to include risk of hypercalcaemia following discontinuation of treatment for giant cell tumour of the bone.

Cases of clinically significant hypercalcaemia complicated by acute renal injury and requiring hospitalization have been reported in a clinical trial of adults and adolescents with giant cell tumour of bone. Cases of rebound hypercalcaemia were reported up to nine months after discontinuation of denosumab.

***Reference:***
Drug Safety Update, MHRA, 22 June 2018 *(www.gov.uk/mhra)*

*(See WHO Pharmaceuticals Newsletters No.3, 2013: Severe hypocalcaemia in Australia; No.1, 2013: Fatal cases of severe symptomatic hypocalcaemia in UK; No.4, 2012: Risk of severe symptomatic hypocalcemia, including fatal cases in Canada)*

## Dipeptidyl peptidase-4 (DPP-4) Inhibitor

### Risk of pemphigoid

**Japan**. MHLW and PMDA have announced that the package inserts for omarigliptin (Marizev®), trelagliptin succinate (Zafatek®), and saxagliptin hydrate (Onglyza®) will be revised to include pemphigoid as a clinically significant adverse reaction.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are indicated for type 2 diabetes mellitus.

A total of 19 cases of pemphigoid associated with the use of DPP-4 were reported during the previous three fiscal years. Of the 19 cases, a causal relationship with DDP-4 inhibitors could not be excluded in six cases.

Based on the investigation of the evidence currently available, MHLW/PMDA concluded that revision of the package inserts was necessary.

***Reference:***
Revision of Precautions, MHLW/PMDA, 19 April 2018 *(www.pmda.go.jp/english/)*

## Eftrenonacog alfa

### Risk of shock and anaphylaxis

**Japan**. MHLW and PMDA have announced that the package insert for eftrenonacog alfa (Alprolix®) should be revised to include shock and anaphylaxis as clinically significant adverse reactions.

Eftrenonacog alfa is used to inhibit bleeding in patients with blood coagulation factor IX deficiency.

One case involving shock and anaphylaxis was reported, and a causal relationship with the product could not be excluded for this case.

Based on the investigation of the evidence currently available, MHLW/PMDA have concluded that the revision of the package insert was necessary.

***Reference:***
Revision of Precautions, MHLW/PMDA, 19 April 2018 *(www.pmda.go.jp/english/)*

## Everolimus

### Risk of impaired wound healing

**Japan**. MHLW and PMDA have announced that the package insert of everolimus (Afinitor®) should be revised to include impaired wound healing as a clinically significant adverse reaction.

Everolimus is indicated for unresectable or metastatic renal cell carcinoma, and neuroendocrine tumor.

The decision to revise the label followed the revision of the product label for another everolimus product called Certican®.

***Reference:***
Revision of Precautions, MHLW/PMDA, 19 April 2018 *(www.pmda.go.jp/english/)*

## Fluoroquinolone antibiotics

### Strengthened warnings on the risk of hypoglycaemia and mental health adverse effects

**USA**. The FDA has announced that the drug labels of fluoroquinolone antibiotics should be strengthened to include coma as a potential outcome of hypoglycaemia, and to list adverse effects related to mental health such as disorientation and agitation.

Fluoroquinolone antibiotics, such as moxifloxacin, delafloxacin, ciprofloxacin, are indicated to treat certain serious bacterial infections.

Most fluoroquinolone antibiotic product labels include a warning on blood sugar disturbances and mental health adverse effects, but the new label changes will add that hypoglycaemia can lead to coma and will also make the mental health adverse effects more prominent and consistent by listing adverse effects such as disturbances in attention, disorientation, and agitation.

***Reference:***
Safety Alerts for Human Medical Products, US FDA, 10 July 2018 *(www.fda.gov)*

*(See WHO Pharmaceuticals Newsletters No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in USA; No.3, 2016: Restricting use in USA)*

## Granulocyte-colony stimulating factor (G-CSF) drugs

### Risk of large vessel vasculitis

**Japan**. MHLW and PMDA have announced that the package inserts of products containing granulocyte-colony stimulating factor (G-CSF) i.e. filgrastim (Gran®, Filgrastim BS®), pegfilgrastim (G-Lasta®), and lenograstim (Neutrogin®) should be revised to include large vessel vasculitis as a clinically significant adverse reaction.

G-CSF products are indicated for prevention of chemotherapy-induced febrile neutropenia and mobilization of hematopoietic stem cells to peripheral blood.

A total of 20 cases involving large vessel vasculitis were reported, and a causal relationship with the products could not be excluded for 14 of these cases.

Based on an investigation of the current available evidence, MHLW/PMDA concluded that revision of the package insert was necessary.

***Reference:***
Revision of Precautions, MHLW/PMDA, 19 April 2018 *(www.pmda.go.jp/english/)*

*(See WHO Pharmaceuticals Newsletters No.3, 2014: Risk of Capillary Leak Syndrome (CLS) in Canada)*

that a combination of additional measures is implemented.

HES solutions for infusion are used for the management of hypovolaemia (low blood volume), where treatment with alternative infusion solutions alone is not considered sufficient.

Because of the risk of kidney injury and mortality, HES solutions for infusion are contraindicated in patients with sepsis or in critically ill patients. In January 2018, PRAC recommended suspending the marketing authorizations because the product continued to be used in those patients. However, the European Commission (EC) requested that the PRAC and the CMDh further consider possible unmet medical needs that could be caused by the suspension.

The CMDh has now concluded that HES solutions for infusion should remain on the market provided that a combination of additional measures is implemented. One of the new measures is a controlled access programme by the marketing authorization holders to ensure that only accredited hospitals will be supplied with the products. Another measure is packaging warnings that remind health-care professionals that these products must not be used in patients with sepsis or kidney impairment or in critically ill patients.

## Ibrutinib

### Potential risk of ventricular tachyarrhythmia

**Canada**. Health Canada has worked with manufacturers to update the product safety information for ibrutinib (Imbruvica®) to include ventricular tachyarrhythmia.

Ibrutinib is indicated for the treatment of bone marrow and white blood cell cancers. It is also used in patients who suffer from refractory chronic graft versus host disease after receiving transplanted tissue from a donor.

Health Canada has received five Canadian reports and examined 150 international reports of ventricular tachyarrhythmia suspected to be linked to ibrutinib.

Health Canada's review concluded that there may be a link between the use of ibrutinib and the risk of ventricular tachyarrhythmia.

***Reference:***
Summary Safety Review, Health Canada, 26 July 2018 (*www.hc-sc.gc.ca*)

*(See WHO Pharmaceuticals Newsletters No.6, 2017: Risk of ventricular tachyarrhythmia, hepatitis B reactivation and infection in Australia; No.5, 2017: Reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and opportunistic infections in UK)*

## Immunosuppressive