World Health Organization

# WHO Pharmaceuticals NEWSLETTER

2019
No. 1

***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,***

*EMP-HIS,*
*World Health Organization,*
*1211 Geneva 27, Switzerland,*
*E-mail address:* pvsupport@who.int

*This Newsletter is also available at:*
http://www.who.int/medicines

The WHO Pharmaceuticals Newsletter provides you with the latest information on 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 the Recommendations from the 41st Annual Meeting of Representatives of the National Pharmacovigilance Centres Participating in the WHO Programme for International Drug Monitoring.

## Contents

**Suggested citation**. WHO Pharmaceuticals Newsletter No.1, 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**

# Table of Contents

## Regulatory Matters



## Safety of medicines



## Signal

# Table of Contents

## Feature

## Aluminium potassium sulfate hydrate/tannic acid

### Risk of anaphylaxis

**Japan**. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for aluminium potassium sulfate hydrate/tannic acid (Zione Injection®) should be revised to include anaphylaxis as an adverse drug reaction.

Aluminium potassium sulfate hydrate/tannic acid is indicated for prolapsed internal haemorrhoids.

Six cases involving anaphylaxis have been reported in patients treated with aluminium potassium sulfate hydrate/tannic acid in Japan during the previous three fiscal years. For five of the six cases a causal relationship with the product could not be ruled out.

MHLW/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, 27 November 2018 *(www.pmda.go.jp/english/)*

## Asunaprevir and daclatasvir

### Risk of renal impairment

**Japan**. The MHLW and the PMDA have announced that the package inserts for asunaprevir (Sunvepra®), and preparations containing daclatasvir (Daklinza® and Ximency®) should be revised to include renal impairment as an adverse drug reaction.

Asunaprevir and daclatasvir are indicated for the improvement of viremia in patients with chronic hepatitis C serogroup 1 or with compensated cirrhosis type C serogroup.

18 cases of renal impairment have been reported in patients who took asunaprevir or daclatasvir in Japan during the previous three fiscal years. In five of these cases a causal relationship with the product could not be excluded.

The MHLW/PMDA concluded that the revision of the package inserts was necessary based on the results of the investigation of the currently available evidence.

***Reference:***
Revision of Precautions, MHLW/PMDA, 10 January 2019 *(www.pmda.go.jp/english/)*

## Atorvastatin and antivirals: interaction

### Increase in atorvastatin plasma levels

**Egypt**. The Egyptian Pharmaceutical Vigilance Center (EPVC) has announced that the product information for atorvastatin will be updated to include a warning about the potential increase in atorvastatin levels when co-administered with elbasvir/grazoprevir and glecaprevir/pibrentasvir. The combined use of glecaprevir/pibrentasvir with atorvastatin is now contra-indicated.

Atorvastatin is a synthetic lipid-lowering agent indicated for the prevention of cardiovascular diseases and hypercholesterolaemia. Elbasvir/grazoprevir and glecaprevir/pibrentasvir preparations are indicated for the treatment of hepatitis C (HCV).

Risk of myopathy may be increased with the concomitant use of atorvastatin and antivirals for treatment of HCV.

***Reference:***
Newsletter, EPVC, December 2018 *(www.epvc.gov.eg)*

## Axitinib

### Risk of interstitial lung disease

**Japan**. The MHLW and the PMDA have announced that the package insert for axitinib (Inlyta®) should be revised to include interstitial lung disease as an adverse drug reaction.

Axitinib is indicated for the treatment of unresectable metastatic renal cell carcinoma.

A total of 20 cases involving interstitial lung disease have been reported in patients treated with axitinib in Japan during the previous three fiscal years. A causal relationship with the product could not be excluded in two of these cases.

MHLW/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, 10 January 2019 *(www.pmda.go.jp/english/)*

## Calcitriol injection

### Risk of shock and anaphylaxis

**Japan**. The MHLW and the PMDA have announced that the package insert for the injectable form of calcitriol (Rocaltrol Injection®) should be revised to include shock and anaphylaxis as adverse drug reactions.

Calcitriol is indicated for secondary hyperparathyroidism in patients undergoing maintenance renal dialysis.

A total of four cases involving shock or anaphylaxis have been reported in patients

treated with injectable calcitriol in Japan during the previous three fiscal years. A causal relationship with the product could not be ruled out in one of the cases.

MHLW/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, 27 November 2018 *(www.pmda.go.jp/english/)*

## Denosumab

### Risk of new primary malignancy (NPM)

**Singapore.** The Health Sciences Authority (HSA) has announced that the package insert for denosumab (Xgeva®) is in the process of being updated to include the incidence of new primary malignancy (NPM) as an adverse reaction.

Denosumab is a human monoclonal antibody (IgG2) indicated for the prevention of skeletal related events (e.g. pathological fracture and spinal cord compression).

During a routine review of denosumab in February 2018, the European Medicines Agency (EMA) noted that NPM was reported more frequently in patients with advanced bone malignancies treated with denosumab compared to zoledronic acid. Although the absolute differences in event rates were small and a clear causal mechanism has not been identified, the EMA could not exclude that there is a potential mechanism linked to an impaired immune response with the use of denosumab.

The HSA has not received any national adverse event reports for NPM associated with the use of denosumab.

***Reference:***
Product Safety Alerts, HSA, 28 December 2018 (*http://www.hsa.gov.sg/*)

*(See WHO Pharmaceuticals Newsletter No.4, 2018: Risk of new primary malignancies in UK)*

## Direct-acting antivirals for chronic hepatitis C

### Risk of hypoglycaemia in patients with diabetes

**United Kingdom.** The Medicines and Healthcare Products Regulatory Agency (MHRA) is updating the Summary of Product Characteristics and Patient Information Leaflets for direct acting antivirals (e.g. daclatasvir (Daklinza®), sofosbuvir/velpatasvir (Epclusa®) and ledipasvir/sofosbuvir (Harvoni®)), to include safety advice to minimise the risk of hypoglycaemia in patients taking medicines for diabetes.

Studies show that some diabetic patients, initiating direct-acting antiviral therapy for chronic hepatitis C infection, have experienced hypoglycaemia. This was confirmed in an EU review.

Glucose levels should be monitored closely in patients with diabetes during direct-acting antiviral therapy for hepatitis C and medicines should be modified when necessary.

***Reference:***
Drug Safety Update, MHRA, 18 December 2018 (*www.gov.uk/mhra*)

*(See WHO Pharmaceuticals Newsletter No.2, 2018: Possible effects on blood glucose control when used in patients with type 2 diabetes in New Zealand; No.2, 2017: Possible effects on blood glucose control when used in patients with type 2 diabetes: added to the medicine monitoring scheme in New Zealand)*

## Emollients

### Risk of severe and fatal burns

**United Kingdom.** The MHRA has announced that the outer packaging and product containers for paraffin-based emollients should include fire hazard warnings. The Summary of Product Characteristics will also be updated to include warnings about the risk of severe and fatal burns.

Patients who use paraffin-based emollients, regardless of the paraffin concentration, should not smoke or go near naked flames because clothing or fabric such as bedding or bandages that have been in contact with an emollient or emollient-treated skin can rapidly ignite.

Emollients are an important and effective treatment for chronic dry skin conditions. The emollient products are not flammable, but they can increase the speed of ignition and intensity of fire if fabric containing dried residue is ignited.

The MHRA is aware of 11 cases in which paraffin-based emollients are suspected to have contributed to an increase in the speed and intensity of a fire, resulting in fatal burns injury. There are also 50 fire incidents (49 fatal) reported by Fire and Rescue Services across the UK between 2000 and November 2018, but in most of these it is not clear what the attributable role of paraffin creams were in the deaths.

***Reference:***
Drug Safety Update, MHRA, 18 December 2018 (*www.gov.uk/mhra*)

*(See WHO Pharmaceuticals Newsletter No.3, 2013: May cause skin irritation, particularly in children with eczema in UK)*

## Fluoroquinolone antibiotics

### 1. Risk of tendon damage and neuropathies

**Ireland.** The Health Products Regulatory Authority (HPRA) has updated the Summary of Product Characteristics (SmPC) and Package Leaflets (PL) for all fluoroquinolone antibiotics to include tendonitis, tendon rupture, neuropsychiatric effects and neuropathies associated with paraesthesia as adverse reactions. The update followed conclusions from a recent review by EMA's Pharmacovigilance Risk Assessment Committee (PRAC)'s.

Fluoroquinolones are a class of broad spectrum antibiotics and include ciprofloxacin, levofloxacin, ofloxacin and moxifloxacin.

The PRAC recommended that fluoroquinolone antibiotic use should be further restricted, and the information provided to patients on potential adverse reactions should be expanded to emphasize the possibility of persisting effects.

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

*(See WHO Pharmaceuticals Newsletter No.6, 2018: Risk of long-lasting and disabling effects in Europe; No.4, 2018: Strengthened warnings on the risk of hypoglycaemia and mental health adverse effects in USA; No.2, 2017: Potential risk of persistent and disabling side effects in Canada; No.1, 2017: Risk of retinal detachment in Singapore; 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; No.1, 2016: Risk of retinal detachment in Canada)*

### 2. Risk of aortic aneurysm and aortic dissection

**Japan**. The MHLW and the PMDA have announced that the package inserts for fluoroquinolones (e.g. moxifloxacin (Avelox®), levofloxacin (Cravit®), ofloxacin (Tarivid®)) should be revised to include aortic aneurysm and aortic dissection as adverse drug reactions.

Results of several epidemiological studies and a non-clinical study have suggested an association between fluoroquinolone use and development of aortic aneurysm or aortic dissection.

Although no cases involving aortic aneurysm or aortic dissection have been reported in Japan during the previous three fiscal years, MHLW/PMDA concluded that revision of the package inserts was necessary based on the opinions of the expert advisors.

Patients should be carefully monitored and instructed to seek medical attention immediately if they experience symptoms such as pain in the abdomen, chest or back. Imaging assessment should be considered if necessary, for patients at risk.

***Reference:***
Revision of Precautions, MHLW/PMDA, 10 January 2019 *(www.pmda.go.jp/english/)*

*(See WHO Pharmaceuticals Newsletter No.6, 2018: Potential risk of aortic aneurysm and dissection in UK)*

## Hydrochlorothiazide

### Risk of non-melanoma skin cancer

**Egypt**. The EPVC has announced that the Summary of Product Characteristics and Package Leaflet for hydrochlorothiazide will be updated to include the risk of non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) as an adverse reaction.

Hydrochlorothiazide is widely used to treat hypertension, cardiac, hepatic and nephrogenic oedema or chronic heart insufficiency.

Pharmacoepidemiological studies have shown an increased risk of non-melanoma skin cancer with exposure to increasing cumulative doses of hydrochlorothiazide.

Patients taking hydrochlorothiazide should be informed of the risk and advised to regularly check their skin. Also, patients should be advised to limit exposure to sunlight and UV rays, and suspicious skin lesions should be examined, potentially by performing histological examinations of biopsies.

***Reference:***
Newsletter, EPVC, December 2018 *(www.epvc.gov.eg)*

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

## Hydrocortisone (muco-adhesive buccal tablets)

### Risk of insufficient cortisol absorption and life-threatening adrenal crisis

**United Kingdom.** The MHRA has updated the product information for hydrocortisone muco-adhesive buccal tablets, to include warnings about the serious risks associated with off-label use for the treatment of adrenal insufficiency in children. Adrenal insufficiency can potentially occur due to insufficient cortisol absorption which can lead to adrenal crisis in stress situations.

Hydrocortisone muco-adhesive buccal tablets are indicated only for local use in the mouth for aphthous ulceration (mouth ulcers).

There are oral formulations of hydrocortisone authorized for the treatment of adrenal insufficiency. Prescribers and pharmacists should only use the licensed products.

***Reference:***
Drug Safety Update, MHRA, 18 December 2018 *(www.gov.uk/mhra)*

## Infliximab

### Risk of mycosis fungoides

**Australia**. The Therapeutic Goods Administration (TGA) has announced that product information for infliximab (Remicade®) is being updated with new information relating to mycosis fungoides.

Infliximab is indicated for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis.

The TGA identified a safety signal based on three local reports of adverse events. The number of observed reports of mycosis fungoides with the use of infliximab is higher than expected. After further analysis of the signal, the TGA is working with the sponsor of infliximab to add information about this condition to the adverse effects section of the product information.

***Reference:***
Medicines Safety Update, TGA, Vol. 9, No. 4, December 2018 (*www.tga.gov.au*)

*(See WHO Pharmaceuticals Newsletter No.4, 2018: Potential risk of linear IgA bullous dermatosis in Canada; No.6, 2015: Limited evidence: risk of cancer (lymphoma, hepatosplenic T-Cell lymphoma, and leukaemia) in Canada; No.5, 2015: Risk of non-melanoma skin cancers, particularly in psoriasis patients in Australia)*

## Lenalidomide

### Risk of progressive

relapsed or refractory adult T-cell leukemia/lymphoma.

There were no cases of PML reported in patients treated with lenalidomide in Japan in the previous three fiscal years. Three cases have been reported overseas, and MHLW/PMDA have concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Patients should be closely monitored during and after the administration of lenalidomide. If symptoms such as disturbed consciousness, cognitive disorder, paralysis, or disorders related to linguistic capacity are observed, administration of this drug should be discontinued, diagnostic assessment using MRI and cerebrospinal fluid tests should be performed, and other measures should be taken as appropriate.

***Reference:***
Revision of Precautions, MHLW/PMDA, 10 January 2019 *(www.pmda.go.jp/english/)*

## Nusinersen

### Risk of hydrocephalus

**Japan**. The MHLW and the PMDA have announced that the package insert for nusinersen (Spinraza Intrathecal Injection®) should be revised to include hydrocephalus as an adverse drug reaction

of the currently available evidence.

***Reference:***
Revision of Precautions, MHLW/PMDA, 10 January 2019 *(www.pmda.go.jp/english/)*

*(See WHO Pharmaceuticals Newsletter No.6, 2018: Potential risk of communicating hydrocephalus in UK)*

## Varicella vaccine (freeze-dried live attenuated)

### Risk of aseptic meningitis

**Japan**. The MHLW and the PMDA have announced that the package insert for freeze-dried live attenuated varicella vaccine (Biken®) should be revised to include aseptic meningitis as an adverse reaction.

Freeze-dried live attenuated varicella vaccine is indicated for prevention of varicella and herpes zoster in patients aged 50 years and older.

A total of two cases of aseptic meningitis have been reported in patients vaccinated with freeze-dried live attenuated varicella vaccine in Japan during the previous three fiscal years. A causal relationship with the product could not be ruled out in one of the cases.

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