



World Health  
Organization

# WHO Pharmaceuticals NEWSLETTER

2017

No. 3

**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 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 two feature articles: Pilot Mobile 'APP' for reporting suspected adverse drug reactions launched in Burkina Faso and Zambia, and, Introducing a New Member in the WHO Programme for International Drug Monitoring (WHO PIDM): Paraguay.

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Printed in Switzerland

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## Bevacizumab

### Potential risk of non-mandibular osteonecrosis in adult cancer patients

**Canada.** Health Canada recommends that the product safety information for bevacizumab (Avastin®) is updated to include information on the potential risk of non-mandibular osteonecrosis in adult cancer patients.

Bevacizumab, when used alone, is used for the treatment of glioblastoma. It can also be used with other chemotherapy medicines to treat cancers of the large bowel, lung, female reproductive system and the lining of the abdominal cavity.

Health Canada initiated a review of the risk of non-mandibular osteonecrosis in adult cancer patients treated with bevacizumab following the publication of two reports in the literature.

At the time of the review, Health Canada had received one report of non-mandibular osteonecrosis related to bevacizumab use. There was insufficient information to conclude that the use of bevacizumab alone had caused this condition in this report.

Health Canada also looked at information on 67 international reports of non-mandibular osteonecrosis related to the use of bevacizumab, including the two cases that triggered the safety review. In 26 of these reports, a link between bevacizumab and non-mandibular osteonecrosis could not be ruled out. In the remaining 41 reports, there were either not enough information to establish a link, or there were confounding factors such as the presence of other bone conditions or treatments known to cause bone damage.

After reviewing available data, it was determined that there is not enough information to establish a definitive link between the use of

bevacizumab and non-mandibular osteonecrosis in adult cancer patients. However, Health Canada has decided to recommend updating the product safety information of bevacizumab to include information on the potential risk.

#### Reference:

Summary Safety Review, Health Canada, 5 April 2017 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

## Canagliflozin

### Increased risk of leg and foot amputations

**USA.** The US Food and Drug Administration (FDA) has requested that the product label for canagliflozin (Invokana® and Invokamet®) is updated to include the risk of leg and foot amputations.

Canagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor and is used with diet and exercise to lower blood sugar in adults with type-2 diabetes.

Final results from two clinical trials - the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type-2 Diabetes Mellitus) - showed that leg and foot amputations occurred twice as often in patients treated with canagliflozin compared to patients treated with placebo.

#### Reference:

Drug Safety Communication, US FDA, 16 May 2017 ([www.fda.gov](http://www.fda.gov))

(See WHO Pharmaceuticals Newsletters No.2, 2017: Risk of lower limb amputation in Malaysia and Potential risk of toe amputation with SGLT inhibitors in the EU and No.3, 2016: Risk of leg and foot amputations: under investigation in the USA)

## Caspofungin

### Risk of Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson syndrome

**Japan.** The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for caspofungin (Cancidas®) has been updated to include the risk of Toxic Epidermal Necrolysis (TEN) and oculomucocutaneous syndrome (Stevens-Johnson syndrome) as clinically significant adverse reactions.

Caspofungin is indicated for febrile neutropenia suspected to be caused by a fungal infection, and for the treatment of fungal infections due to *Candida* or *Aspergillus*.

The update followed reports of TEN and/or oculomucocutaneous syndrome in patients treated with caspofungin both in Japan and overseas, and following revision of the company core datasheet (CCDS) and package inserts in the United States and Europe.

#### Reference:

Revision of Precautions, MHLW/PMDA, 20 April 2017 ([www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

## Clopidogrel

### Potential risk of spinal haematoma, cholecystitis and haematemesis

**Republic of Korea.** The Ministry of Food and Drug Safety (MFDS) has announced that the label for clopidogrel has been revised to include spinal haematoma, cholecystitis and haematemesis as adverse reactions.

Clopidogrel is a platelet aggregation inhibitor and is indicated for the reduction of the rate of cardiovascular death, myocardial infarction,

and stroke in patients with acute coronary syndrome.

At the time of review, the Korea Institute of Drug Safety and Risk Management (KIDS) had received three domestic reports of spinal haematoma, nine domestic and eight international reports of cholecystitis, and six domestic and 24 international reports of haematemesis with clopidogrel through Korea Adverse Event Reporting System (KAERS) from 1989 to 2015. Reports for clopidogrel and spinal haematoma/cholecystitis/haematemesis were identified to be statistically significant compared to all the other reports from other drugs.

This recommendation announced by MFDS was based on signal analysis evaluation process in KIDS using adverse event reports.

**Reference:**

Based on the communication from MFDS and KIDS, Republic of Korea, April 2017

## Codeine and tramadol

### Restriction of use in children and advice against use in breastfeeding women

**USA.** The US FDA has changed the labels of prescription medicines containing codeine and tramadol to inform of the restriction of use in children and recommend against the use of codeine and tramadol medicines in breastfeeding mothers due to risk of serious adverse reactions in breastfed infants. These adverse reactions include excess sleepiness, difficulty breastfeeding or serious breathing problems that could result in death.

Codeine and tramadol are approved to treat pain, and codeine is also approved to treat cough.

The FDA reviewed adverse event reports submitted to the FDA from January 1969 to May

2015 and identified 64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years. Nine cases of serious breathing problems, including three deaths, with the use of tramadol in children younger than 18 years from January 1969 to March 2016 were also identified. The majority of serious adverse effects with both codeine and tramadol occurred in children younger than 12 years, and some cases occurred after a single dose of the medicine.

In a review of the medical literature the FDA found numerous cases of excess sleepiness and serious breathing problems in breastfed infants, including one death. A review of the available medical literature for data regarding tramadol use during breastfeeding did not reveal any cases of adverse events. However, tramadol and its active form are also present in breast milk, and tramadol has the same risks associated with ultra-rapid metabolism as codeine.

**Reference:**

Drug Safety Communication, US FDA, 20 April 2017 ([www.fda.gov](http://www.fda.gov))

(See WHO Pharmaceuticals Newsletters No.2 and No.1, 2017, No.6 and No.1 in 2016, No.6, No.5, No.4 and No.3 in 2015, No.5 and No.4 in 2013, and No.5 in 2012 for related information)

## Denosumab

### Risk of multiple vertebral fractures

**Japan.** The MHLW and the PMDA have announced that the package insert for denosumab (Pralia®) has been updated to include the risk of multiple vertebral fractures as a clinically significant adverse reaction. The MHLW/PMDA have also advised transitioning to an alternative antiresorptive medicine if treatment with denosumab is discontinued, to

prevent multiple vertebral fractures that can occur due to a temporary increase in bone resorption.

Denosumab is indicated for osteoporosis.

Off-treatment follow-up results of overseas clinical studies showed a higher incidence of multiple new vertebral fractures in patients who discontinued denosumab compared with those who discontinued placebo which led to the revision of the company core data sheet (CCDS). In addition, overseas pre-market clinical studies showed a temporary increase in bone resorption after discontinuation of denosumab treatment. The time to onset of the multiple new vertebral fractures after discontinuation of denosumab treatment found in the studies was consistent with the time to onset of the temporary increase in bone resorption. Based on these findings, the MHLW/PMDA concluded that updating the package insert is necessary.

**Reference:**

Revision of Precautions, MHLW/PMDA, 20 April 2017 ([www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

## Dipeptidylpeptidase-4 (DPP-4) inhibitors

### Risk of arthralgia

**Canada.** Health Canada has updated the product safety information for all dipeptidylpeptidase-4 (DPP-4) inhibitors to include information on the risk of arthralgia (severe joint pain).

DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin and sitagliptin) are used to treat type-2 diabetes in adults. They are used along with an appropriate diet and exercise to control blood sugar. In some cases, they are used with another anti-diabetic drug.

Health Canada reviewed the potential risk of arthralgia with

the use of DPP-4 inhibitors following the identification of reports of adverse effects in the published literature and in the US FDA Adverse Event Reporting System (FAERS) database.

At the time of the review, Health Canada received 10 Canadian reports of severe joint pain and 20 international reports from the manufacturers associated with the use of a DPP-4 inhibitor (saxagliptin, sitagliptin or linagliptin).

Of all the reports, 17 noted that the patient developed joint pain within the first 30 days of taking the DPP-4 inhibitor. The majority of patients either improved or recovered from their joint pain after the treatment was stopped.

Some of the cases have also reported medical conditions that may have contributed to the joint pain including gout, pre-existing rheumatoid arthritis, Crohn's disease and obesity.

Health Canada's review of the available information concluded there is a potential link between the use of DPP-4 inhibitors and the development of severe joint pain.

#### **Reference:**

Summary Safety Review, Health Canada, 27 April 2017 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

(See WHO Pharmaceuticals Newsletters No.6, 2015: Risk of severe joint pain in Egypt and No.5, 2015: DPP-4 inhibitors for Type 2 diabetes may cause severe joint pain in the USA)

## **Factor VIII medicines**

### **No clear evidence to suggest a difference in inhibitor development between plasma-derived and recombinant products**

**EU.** The European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the prescribing information of

factor VIII medicines should be updated to reflect the conclusion that there is no clear and consistent evidence of a difference in inhibitor development between classes of factor VIII medicines.

Factor VIII products replace the missing factor VIII in patients with haemophilia. Human plasma-derived factor VIII medicines are extracted from blood plasma. Recombinant factor VIII is produced from DNA technology. The body may develop inhibitors as a reaction to these medicines, particularly in patients starting treatment for the first time.

The review was started following a study which concluded that inhibitors develop more frequently in patients receiving recombinant factor VIII medicines than in those receiving plasma-derived factor VIII medicines.

The review included relevant studies which differed in their design, patient populations and findings, and the PRAC concluded that they did not provide clear evidence of a difference in the risk of inhibitor development between the two classes of factor VIII medicines.

In addition, due to the different characteristics of individual products within the two classes, the PRAC considered that evaluation of the risk of inhibitor development should be at the product level instead of at the class level. The risk for each individual product will continue to be assessed as more evidence becomes available.

#### **Reference:**

News and press release, EMA, 5 May 2017 ([www.ema.europa.eu](http://www.ema.europa.eu))

(See WHO Pharmaceuticals Newsletter No.3, 2013: Review on the benefits and risks in previously untreated patients with haemophilia A with Kogenate® and Helixate® started in the EU)

## **General anaesthetic and sedation drugs**

### **Potential risk of effects on development of children's brains**

**USA.** The US FDA has announced that the labels for general anaesthetic and sedation medicines will be updated to include information on potential effects on brain development in children younger than three years. The updated label changes include:

- A new warning stating that exposure to anaesthetic and sedation medicines for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than three years.
- Additional information describing results of animal studies in pregnancy and the young. Exposure to general anaesthetic and sedative medicines for more than three hours can cause widespread loss of nerve cells in the developing brain, resulting in long-term negative effects on the animal's behaviour or learning in young animals.

Anaesthetic and sedative medicines are necessary for infants, children and pregnant women who require surgery or other painful and stressful procedures. In addition, untreated pain can be harmful to children and their developing nervous systems.

#### **Reference:**

Drug Safety Communication, US FDA, 27 April 2017 ([www.fda.gov](http://www.fda.gov))

(See WHO Pharmaceuticals Newsletter No.1, 2017: Potential risk of effects on development of children's brains in the USA)

## Ingenol mebutate

### 1. Risk of hypersensitivity reactions, herpes zoster and eye injury

**Australia.** The Therapeutic Goods Administration (TGA) has updated the Product Information for ingenol mebutate (Picato gel®) to add warnings of hypersensitivity reactions, herpes zoster and ophthalmic injury as precautions and adverse effects.

Ingenol mebutate is indicated in actinic keratosis.

The TGA investigated safety concerns relating to ingenol mebutate following reports of severe allergic reactions, herpes zoster, ophthalmic injury and local skin reactions in the United States. Some of these cases were associated with the medicine not being used in accordance with its directions for use.

The TGA investigation found that the risk of local skin reactions was well-communicated in the Product Information. However, the Product Information did not address the potential adverse events of hypersensitivity/anaphylaxis, herpes zoster reactivation or, ophthalmic injury.

#### Reference:

Medicines Safety Update, TGA, Vol. 8, No. 2, April-May 2017 ([www.tga.gov.au](http://www.tga.gov.au))

(See WHO Pharmaceuticals Newsletter No.5, 2015: Risk of severe allergic reactions and herpes zoster (shingles) in the USA)

### 2. Risk of keratoacanthoma

**Ireland.** The Health Products Regulatory Authority (HPRA) has stated that the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for ingenol mebutate (Picato®) will be updated to include information on the risk of keratoacanthoma.

Ingenol mebutate is indicated for the cutaneous treatment of nonkeratotic, non-hypertrophic actinic keratosis in adults, and is available for topical use in different strengths.

There have been reports of keratoacanthoma occurring within the area treated with ingenol mebutate, with a time to onset ranging from weeks to months.

The HPRA has advised health-care professionals to counsel patients to be vigilant for new skin lesions developing within the area treated with ingenol, and to immediately consult their doctor should any occur.

#### Reference:

Drug Safety Newsletter, HPRA, March 2017

## Interferon alfa and interferon beta

### Risk of pulmonary arterial hypertension (PAH)

**Malaysia.** The National Pharmaceutical Regulatory Agency (NPRA) has issued instructions to update the package inserts for interferon alpha and interferon beta containing products to include the potential risk of pulmonary arterial hypertension (PAH).

Interferons are a group of glycoproteins that have immunoregulatory, antiviral and antineoplastic functions. Indications include treatment of multiple sclerosis, hepatitis, carcinoma, lymphoma, leukaemia and myeloma.

From year 2002 to January 2016, the NPRA has received 91 ADR reports with 204 adverse events associated with interferon alfa use. Seven reports were related to the System Organ Class (SOC) Respiratory, Thoracic and Mediastinal Disorders and consisted of cough, difficulty in breathing, bloody sputum, nasal congestion and epistaxis.

For interferon beta, a total of 73 ADR reports with 137 adverse events were received by NPRA between 2002 to January 2016. Two reports were associated with the SOC Respiratory, Thoracic and Mediastinal Disorders, namely difficulty in breathing and sneezing.

Whilst there were no reports specifically on PAH, two cases reported patients experiencing symptoms of PAH namely, chest pain (with use of peginterferon alfa-2a) as well as oedema and abdominal distension (with interferon beta-1b).

#### Reference:

Reaksi Drug Safety News, NPRA, No. 34, March 2017

(See WHO Pharmaceuticals Newsletter No.6, 2016: Risk of pulmonary arterial hypertension in Canada)

## Iodinated contrast medium

### Potential risk of hypothyroidism

**Canada.** Health Canada has updated the product safety information for all iodinated contrast medium (ICM) products to include information on potential risk of hypothyroidism in certain patients (mostly infants). In addition, Health Canada will publish a Health Product Risk Communication to inform health-care professionals about this safety information and provide recommendations to monitor thyroid function following ICM use in infants.

ICM products are medical imaging dyes for viewing the insides of different body parts.

At the time of review, Health Canada had not received any Canadian reports of ICM and hypothyroidism.

The safety review examined 23 international reports of adverse effects for hypothyroidism with the use of ICM. Of these, 10



were considered to be related to the use of ICM. In three of the ten reports, the patients recovered and in two reports, the patients did not recover. There were no information provided on recovery of patients for the remaining five reports. Thirteen reports did not contain enough information to determine if the ICM product played a role in the onset of hypothyroidism. While the reports represented patients from all age groups, six of the 10 reports related to ICM-use involved infants (age less than one year).

The review of the scientific literature found a link between ICM use and the potential risk of hypothyroidism. Most of the reports involved infants but adults also experienced this adverse effect.

Health Canada's review concluded that there is a rare potential risk of hypothyroidism with the use of ICM in certain patients, mostly infants.

**Reference:**

Summary Safety Review, Health Canada, 24 April 2017 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

*(See WHO Pharmaceuticals Newsletters No.2, 2017: Possible risk of hypothyroidism in infants: added to the medicines monitoring scheme and No.6, 2015: Rare cases of underactive thyroid in infants in the USA)*

**Pembrolizumab**

**Risk of myocarditis**

**Japan.** The MHLW and the PMDA have announced that the package insert for pembrolizumab (Keytruda®) has been updated to include the risk of myocarditis as a clinically significant adverse reaction.

Pembrolizumab is used for treatment of unresectable malignant melanoma and unresectable, advanced or recurrent programmed death ligand 1 (PD-L1) positive non-small cell lung cancer.

The update was due to cases of myocarditis reported overseas and the revision of the company core data sheet (CCDS).

**Reference:**

Revision of Precautions, MHLW/PMDA, 20 April 2017 ([www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

**Ticagrelor**

**Potential risk of pulmonary haemorrhage**

**Republic of Korea.** The MFDS has announced that the label for ticagrelor has been revised to include pulmonary haemorrhage as an adverse reaction.

Ticagrelor is used as a platelet aggregation inhibitor.

Ticagrelor is administered with aspirin and indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome.

At the time of review, the KIDS had received three domestic and six international reports of pulmonary haemorrhage with ticagrelor through KAERS from 1989 to 2015. Reports for ticagrelor and pulmonary haemorrhage were identified to be statistically significant compared to all the other reports from other drugs.

This recommendation announced by MFDS was based on a signal analysis evaluation process in KIDS using adverse events reports.

**Reference:**

Based on the communication from MFDS and KIDS, Republic of Korea, April 2017

**Valproate**

**Risk of developmental disorders**

**The United Kingdom.** The Medicines and Healthcare Products Regulatory Agency

(MHRA) has sent a Patient Safety Alert highlighting risks of developmental disorders in unborn children. The alert directs organisations to undertake systematic identification of women and girls taking valproate and to support them to make informed choices.

Valproate (Epilim® and Depakote®), also known as valproic acid, is an effective medication used to treat epilepsy and bipolar disorder.

Evidence suggests around one in five women taking valproate are not aware of risks in pregnancy. Evidence from the Clinical Practice Research Datalink also suggests that the measures put in place to increase awareness of risks in pregnancy have not had a significant effect.

In March 2017, the European PRAC initiated a further review to look at the use of valproate-containing medicines in females of childbearing potential. The committee will consider whether these medicines require further restrictions of use due to high risk of developmental disorders and congenital malformations in unborn babies, and the continued use of valproate during pregnancy. The review will also examine the effectiveness of regulatory measures put in place to increase awareness and reduce valproate use in patients at risk.

**Reference:**

Drug Safety Update, MHRA, Volume 10, issue 9:1, April 2017 ([www.gov.uk/mhra](http://www.gov.uk/mhra))

*(See WHO Pharmaceuticals Newsletters No.2, 2016, No.2 and No.1, 2015, No.5, 2014, and No.6 and No.3, 2013 for related information)*

## Crizotinib

### Potential risk of gastrointestinal perforation: not enough evidence

**Canada.** Health Canada has reviewed the potential risk of gastrointestinal perforation with the use of crizotinib (Xalkori®) following safety reports received by the manufacturer.

Crizotinib is authorized to treat specific types of advanced lung cancers.

At the time of the review, Health Canada did not receive any Canadian reports for gastrointestinal perforation related to crizotinib use.

The safety review evaluated information collected by the manufacturer and consisted of 32 international reports of gastrointestinal perforation in the bowel with the use of crizotinib. In general, the reports did not contain enough information to determine if crizotinib use caused the adverse effect. The indication itself is also a risk factor.

While some other products in the same class as crizotinib (e.g. sorafenib, regorafenib and axitinib) have been linked to gastrointestinal perforation, Health Canada's search of the published literature did not find any studies or patient reports of this adverse effect with the use of crizotinib.

Health Canada's review of the available information did not establish a link between the use of crizotinib and gastrointestinal perforation.

#### Reference:

Summary Safety Review, Health Canada, 4 May 2017 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

## Direct-acting antivirals (DAAs)

### 1. Potential risk of liver cancer recurrence: not enough evidence

**Canada.** Health Canada has reviewed the potential risk of liver cancer recurrence with the use of direct-acting antivirals (DAAs).

DAAs are used for the treatment of chronic HCV infection in adult patients, cirrhosis or liver cancer.

At the time of the review, Health Canada had received three Canadian reports of liver cancer recurrence with use of DAAs (two with Sovaldi® and one with Hologic Pak®). All three reports were considered to be related to the use of DAAs. However, other factors present in the cases may have played a role in liver cancer recurrence, such as serious cirrhosis, previous history of liver cancer and other treatments known to be associated with a higher risk of liver cancer recurrence, including surgery and radiofrequency ablation.

The safety review also examined information from 14 international reports of liver cancer recurrence with the use of DAAs: nine reports involved Sovaldi®, four reports involved Harvoni® and one report involved Hologic Pak®. All 14 reports were considered to be related to DAAs use. However, other factors associated with a higher risk of liver cancer were reported.

A search of the scientific literature identified seven relevant studies describing the recurrence of liver cancer with use of DAAs. The role of DAAs in relation to recurrence of liver cancer could not be made because the length of time the patients were monitored were different between studies. The patients in the studies also had a variety of risk factors for liver cancer, including HCV infection,

cirrhosis, previous history of liver cancer and advanced age.

Health Canada's review concluded that there was not enough information to establish a link between DAAs and liver cancer recurrence. Health Canada has also made a request for additional safety information from manufacturers of DAAs regarding this risk as it becomes available.

#### Reference:

Summary Safety Review, Health Canada, 3 May 2017 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

### 2. Potential risk of liver failure

**New Zealand.** The Medicines and Medical Devices Safety Authority (Medsafe) has stated Medsafe is continuing to monitor reports of adverse reactions to DAAs.

The Centre for Adverse Reactions Monitoring (CARM) has received five case reports of liver failure where the reported suspected medicines were included in a DAA regimen. All five cases were in patients with cirrhosis using Viekira Pak-RBV®.

Medsafe advised that patients with cirrhosis who are being treated with Viekira Pak® or Viekira Pak-RBV® should:

- be monitored for clinical signs and symptoms of hepatic decompensation such as ascites, hepatic encephalopathy and variceal haemorrhage
- have hepatic laboratory testing before starting treatment and regularly during treatment
- have their treatment discontinued if they develop evidence of hepatic decompensation.

#### Reference:

Safety Information, Medsafe, 12 May 2017 ([www.medsafe.govt.nz](http://www.medsafe.govt.nz))

## Fluconazole

### 1. Reminder not to use during pregnancy

**Ireland.** The HPRA has provided the following advice to health-care professionals:

- Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.
- Fluconazole in high doses and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Fluconazole is used for treatment and prevention of specified fungal infections in adults and children.

Results of an observational study suggests an increased risk of spontaneous abortion in women taking fluconazole during the first trimester of pregnancy. Previous studies have linked high dose and long-term treatment to birth defects.

#### Reference:

Drug Safety Newsletter, HPRA, March 2017

### 2. Caution in use during pregnancy

**Malaysia.** The NPRA is reviewing the possible association between oral fluconazole exposure during pregnancy and the risk of spontaneous abortion and stillbirth. The NPRA advises cautious prescribing of oral fluconazole in pregnancy until this review is completed.

Since year 2000 to July 2016, the NPRA has received 149 safety reports with 236 adverse events associated with fluconazole. The highest reported adverse events were maculo-papular rash, increased hepatic enzymes, and pruritus. At the time of this communication, there were no reports related to spontaneous abortion or stillbirth.

The NPRA has provided advice for health-care professionals to prescribe oral fluconazole during pregnancy with caution and to consider alternative treatment options, such as clotrimazole for uncomplicated candidiasis.

#### Reference:

Reaksi Drug Safety News, NPRA, No. 34, March 2017

*(See WHO Pharmaceuticals Newsletter No.3, 2016: Risk of miscarriage in pregnancy: under investigation in the USA)*

## Flutamide

### Severe cases of hepatotoxicity with off-label use

**Spain.** La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) recuerda a los profesionales sanitarios que la única indicación autorizada para flutamida es el carcinoma de próstata y que no debe utilizarse en mujeres para el tratamiento de hirsutismo, seborrea, acné y alopecia androgenética.

Flutamida, antiandrógeno oral no esteroideo, está autorizado, en combinación con los agonistas de la hormona liberadora de hormona luteinizante (LHRH), para el tratamiento del carcinoma metastásico de próstata.

El Comité de Seguridad de Medicamentos de Uso Humano (CSMH) de la AEMPS ha evaluado recientemente el uso fuera de indicación de este producto para el tratamiento de la alopecia androgenética en mujeres. La evaluación se ha llevado a cabo a raíz de un caso notificado al Sistema Español de Farmacovigilancia de hepatitis con desenlace mortal en una mujer que recibió tratamiento con flutamida para esta indicación.

En la evaluación se han analizado los casos de notificación espontánea de sospechas de reacciones adversas asociadas a flutamida

procedentes de las bases de datos española (FEDRA), europea (EudraVigilance) y de la OMS (VigiBase), así como los casos publicados en la literatura científica.

La mayoría de los casos de daño hepático asociados a la administración de flutamida se describen en pacientes varones con cáncer prostático. Sin embargo se han identificado casos en mujeres a las que se les prescribió flutamida para el tratamiento de alguno de los cuadros clínicos citados anteriormente.

Entre las alteraciones hepáticas notificadas en estas mujeres, se encuentran casos muy graves que llegaron a requerir trasplante hepático e incluso ocasionaron la muerte de la paciente:

- En España se han notificado hasta la fecha un total de 10 casos de trastornos hepáticos asociados al uso de flutamida en mujeres, ocho de ellos considerados graves. Las reacciones adversas notificadas fueron hepatitis, hepatitis colestásica, esteatosis hepática y elevación de enzimas hepáticas. La indicación para la cual se administró flutamida fue hirsutismo, acné y alopecia androgenética. Ocho de las pacientes se recuperaron mientras que dos requirieron trasplante hepático. Una de las pacientes trasplantadas falleció posteriormente.
- La información de las bases de datos EudraVigilance y VigiBase indica que se han notificado casos de características similares tanto en países europeos como fuera de Europa.
- Diversas publicaciones científicas documentan casos de daño hepático grave asociado al uso de flutamida en mujeres fuera de las condiciones autorizadas.

**Reference:**

Información dirigida a profesionales sanitarios, AEMPS, 27 April 2017, Spain ([www.aemps.gob.es](http://www.aemps.gob.es))

## Multiple sclerosis therapies

### Potential rebound effect after stopping or switching therapy

**The United Kingdom.** The MHRA has reported the publication of two articles that describe a suspected rebound syndrome in patients with multiple sclerosis after cessation of fingolimod (Gilenya®) and/or switching to alternative treatments.

In conjunction with other European national regulatory authorities and the EMA, the MHRA is evaluating all available evidence on this safety signal. Further information on the outcome of the review and relevant new guidance will be issued as soon as it is available.

The MHRA reminded health-care professionals that they should report any suspected adverse effects relating to fingolimod or other treatments for multiple sclerosis, including those that occur after discontinuation.

**Reference:**

Drug Safety Update, MHRA, Volume 10, issue 9:3, April 2017 ([www.gov.uk/mhra](http://www.gov.uk/mhra))

## Ponatinib

### Risk of vascular occlusive events

**The United Kingdom.** The MHRA has issued advice to prescribers about considering dose reduction of ponatinib (Iclusig®) to 15 mg a day for patients with chronic phase chronic myeloid leukaemia (CP-CML) who have achieved a major cytogenetic response.

Ponatinib is used to treat adults with chronic myeloid leukaemia or Philadelphia-chromosome-positive acute lymphoblastic leukaemia. It is restricted to patients who have limited alternative treatment options with tyrosine kinase inhibitors.

In November 2014, the MHRA informed health-care professionals of conclusions from a European-level review of the risk of serious vascular occlusive events with ponatinib and provided advice on minimizing risks. Additional long-term follow-up data are now available which provide further information and support advice on dose modifications to reduce this risk.

The available evidence shows that the risk of arterial occlusion with ponatinib is likely to be dose-dependent and that dose reduction may therefore reduce the risk of life-threatening vascular events.

The recommended starting dose of ponatinib remains at 45 mg once a day for all patients.

**Reference:**

Drug Safety Update, MHRA, Volume 10, issue 9:2, April 2017 ([www.gov.uk/mhra](http://www.gov.uk/mhra))

(See WHO Pharmaceuticals Newsletters No.6 and No.1, 2014 and No.6, 2013 for Related information)

## Testosterone

### Risk of arterial thromboembolism/venous thromboembolism

**Australia.** The TGA has reminded health-care professionals that they should only prescribe testosterone if prescribing is in line with the registered indications and Pharmaceutical Benefits Scheme restrictions.

The TGA has been monitoring testosterone in relation to the risk of arterial thromboembolism/venous thromboembolism since the

publication of a US FDA safety communication in 2014.

As part of the review, the TGA sought advice from the Advisory Committee on the Safety of Medicines (ACSOM). During the meeting on 2 September 2016, ACSOM found that there was a weak signal of increased cardiovascular risks with use of testosterone medications in general (but not for specific events).

The TGA noted this advice, but given there is only a weak signal, the TGA has decided that it is not necessary to update the Product Information documents for testosterone medicines for the time being.

**Reference:**

Medicines Safety Update, TGA, Vol. 8, No. 2, April-May 2017 ([www.tga.gov.au](http://www.tga.gov.au))

(See WHO Pharmaceuticals Newsletter No.4, 2014: Risk of venous blood clots in the USA)

## Viekira PAK® and Technivie® (direct-acting antivirals)

### Interaction with ethinyloestradiol

**Australia.** The TGA has warned that although the Product Information documents for Viekira PAK® and Viekira PAK-RBV® state that use with ethinyloestradiol-containing medicines is a contraindication due to a potential interaction resulting in elevated alanine transaminase (ALT) blood levels, not all ethinyloestradiol-containing medicines currently provide information and precautions regarding this interaction.

Viekira PAK® and Viekira PAK-RBV® are indicated for the treatment of genotype 1 chronic hepatitis C infection, including patients with compensated cirrhosis. Technivie® is used for treatment of adult patients (in combination with ribavirin) with

genotype 4 chronic HCV. Technivie® is not yet marketed in Australia.

The Product Information documents for Viekira PAK® and Viekira PAK-RBV® state that during clinical trials transient, asymptomatic elevations of alanine transaminase (ALT) to greater than five times the upper limit of normal occurred in approximately 1% of all subjects. These ALT elevations were significantly more frequent in female subjects who were using ethinylestradiol-containing medicines. ALT elevations typically occurred during the first four weeks of treatment and declined within approximately two weeks of onset with continued dosing of Viekira PAK® or Viekira PAK-RBV®.

**Reference:**

Medicines Safety Update, TGA, Vol. 8, No. 2, April-May 2017 ([www.tga.gov.au](http://www.tga.gov.au))

A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 15 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC's current routine signal detection process. Signals are first communicated to National Pharmacovigilance Centres through SIGNAL (a restricted document from UMC), before being published in this Newsletter. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 26). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. For more information, visit [www.who-umc.org](http://www.who-umc.org). To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: [signals@who-umc.org](mailto:signals@who-umc.org).

## **Ibrutinib and pneumonitis**

*Dr Birgitta Grundmark, Uppsala Monitoring Centre*

### **Editorial Comment**

Since the finalization of the evaluation of the signal pneumonitis in relation to ibrutinib, the closely related term "interstitial lung disease" (ILD) has been included into the EU SmPC as an acknowledged side effect; hence the signal detected by the UMC has been confirmed by regulatory bodies and the MAH. Advice on appropriate monitoring of patients regarding ILD and on the clinical handling of patients in whom ILD has occurred has also been added.

### **Summary**

Ibrutinib is an antineoplastic substance belonging to the class of protein kinase inhibitors (PKI) where, for the majority of other PKI substances, a causal association between the drugs and pneumonitis or similar respiratory drug reactions, is acknowledged and labelled.

In May 2016, 39 cases of pneumonitis in relation to ibrutinib use had been reported by the countries participating in the WHO Programme for International Drug Monitoring. An evaluation of the reports of pneumonitis in the WHO global database of individual case safety reports, VigiBase, and other data has been performed. Based on the available information, the consistent pattern of the events described in the reports, and our background knowledge of the acknowledged potential of the drug class of PKIs to cause pneumonitis or interstitial lung disease, our conclusion is that for ibrutinib a causal association between the substance and pneumonitis may also exist. We hence consider this signal worth

communicating so that relevant stakeholders may act upon it.

### **Introduction**

In the regular UMC signal detection screening, the combination of ibrutinib and pneumonitis was detected in the first quarter of 2016 as a potential signal.

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (TK). It belongs to the rapidly growing and evolving class of functionally diverse approved protein kinase inhibiting (PKI) drugs. Ibrutinib is currently the only substance with its particular mechanism of action approved for use in humans, although we understand there are others under development. Bruton's TK is a signalling molecule within the B-cell antigen receptor (BCR) and cytokine receptor pathways necessary for B-cell trafficking, chemotaxis and adhesion. The BCR pathway is implicated in several B-cell malignancies, and ibrutinib inhibits malignant B-cell proliferation and survival.<sup>1</sup> The ATC code is L01XE27.

Numerous approaches to target the inhibition of protein kinase (PK) signalling have been explored and developed, e.g. protein and oligonucleotide-based substances targeting growth factor or receptor TK, small-molecule inhibitors targeting unique kinase conformational forms and binding sites. Some substances have very specific kinase selectivity profiles whereas others have a broader mode of action on several PKs.

Approvals for ibrutinib show small differences around the world and include indications in mantle cell lymphoma (MCL), chronic lymphatic leukaemia (CLL) and Waldenström's macroglobulinaemia (WM) with a recommended dose in MCL of 560 mg daily and in CLL and WM of 420 mg daily per os. The treatment may continue until disease progression or until no longer tolerated by the patient.

Pneumonitis is an inflammation of the lung interstitium and/or alveoli. Definitions of, and borders between pneumonitis and closely related terms such as interstitial lung disease (ILD), vary somewhat between authors, languages, and medical traditions. This has become apparent while assessing this signal detected from reports from different countries. Clinically, pneumonitis is most commonly used to describe an inflammation without the presence of an infection, whereas when an infection is present it typically is classified as pneumonia. Common symptoms of pneumonitis are cough and shortness of breath alongside more general symptoms of malaise and fever. Hypoxia may or may not be present. A diagnosis of drug induced pneumonitis is usually reached based on clinical symptoms, X-ray or CT-scan, sometimes biopsy, negative cultures, and the absence and exclusion of other plausible explanations or a positive rechallenge.

Among several causes of pneumonitis are iatrogenic exposure including some antibiotics, chemotherapeutics, anti-arrhythmics and radiation treatments to the chest. Other causes include exposure to mould, bacterial or animal proteins and various chemicals and gases. Pneumonitis may also appear as a symptom of other diseases, e.g. connective tissue diseases and lymphoproliferative disorders. Treatment includes, when possible, removal of the underlying cause of the condition, systemic steroids, and if needed, oxygen and assisted respiration.

In summary, the definitions, aetiology and coding of pneumonitis and similar conditions are diverse.

### Reports in VigiBase

In May 2016, there were 39 reports of pneumonitis in relation to ibrutinib treatment identified in VigiBase, the WHO international database of suspected adverse drug reactions. The reported cases originated from and were entered by national pharmacovigilance centres in four countries: USA (n=20), Italy (n=14), Germany (n=3) and United Kingdom (n=2). The gender of the patients in the reports mirrors the population studied pre-approval (as per the EU SmPC) with 27 men and 9 women. In three cases the gender was not reported. In the 33 reports where age was unambiguously reported, the age range was 46 to 86 years with a mean age of 69 years and a median of 71 years, also mirroring the population in the preapproval clinical trials.

Indication for treatment was reported as CLL in 26 cases, MCL in 7 cases and WM, other specified lymphomas or not given in 4 cases.

Dosages when reported were usually the labelled ones, i.e. 420 or 560 mg daily. The ibrutinib SmPC gives standardized advice for dose reductions in cases of interaction or toxicity.<sup>1</sup> Dose reductions were reported during treatment in a few cases, presumably for interactions or toxicity reasons prior to, or at the time of onset or diagnosis of pneumonitis, although in most reports there is only scant information on the reasons for the dosing revisions.

The recording of any exact time to onset (TTO) would not be expected for any case of pneumonitis due to the natural course of a disease with an often insidious onset. Data on the TTO or time to diagnosis (D) or time to hospitalisation (H) is available with varying degrees of accuracy in most of the reports (n=32). Where there is uncertainty regarding the data, the longest period has been assumed and presented. The range of the TTO/D/H is 2 weeks to 14.5 months with a median of less than 6 months. In eight cases the TTO/D/H was 2 months or less and in three cases the TTO/D/H was 9 months or more.

Only a few reports mention in any detail the diagnostic laboratory methods used. Among methods mentioned are X-ray/CT scan, bronchoscopy, biopsy, BAL and (negative) cultures.

In five cases the outcome was fatal, and in most of these the cause of death was considered by reporters or concluded from the report to be a combination of the reported event(s) and the underlying disease, which would be expected considering the diseases being treated. The pattern of TTO in these cases were similar to the cases in general. Other contributing causes of death in these cases were described as a history of recurrent pneumonitis, sepsis (n=2), cerebral haemorrhage and a "general infective state".

In 16 reports a dechallenge is mentioned before recovery. Many of the reports mention treatment with antibiotics apparently under following a primary diagnosis of pneumonia with fewer mentioning steroid treatment or a need for oxygen treatment for any period of time. Among the reports from Italy, a translation or coding issue cannot be excluded where the coded (English) MedDRA term pneumonitis in Italian could potentially include both pneumonitis and pneumonia ("polmonite"). When clinically detecting and diagnosing pneumonitis, a primary (differential) diagnosis of pneumonia is common and sometimes the two conditions coincide. From the limited data provided, none of the cases could be definitively excluded as

being cases of pneumonia rather than pneumonitis, although in some of them this could be suspected.

Four of the reports include information about a negative rechallenge i.e. where ibrutinib was reinstated with the same (and in some cases a lower) dose without recurrence of the pneumonitis, in some cases with concurrent steroid treatment.

In two of the cases the reporter considered that the underlying disease, rather than ibrutinib, was the more probable cause of the event, which would explain the reaction. In the other two cases, the discovery of pneumonitis appeared to have been a more or less incidental finding, via X-ray and CT respectively, and both of these patients also had a history of several courses of chemotherapy and radiation therapy of the chest, which could have influenced the finding.

Two reports were considered less relevant. They recorded reactions other than pneumonitis in relation to ibrutinib where the patient rather had a history of pneumonitis caused by another drug, apparently mistakenly being coded as a "current" ADR. Another report has been considered "invalid" by the national centre since it only states that the patient "may" have had an ADR and lacks adequate information.

In 11 of the reports, ibrutinib was the only reported drug and in 22 cases it was the only suspected drug. In five cases other drugs were reported alongside ibrutinib for which pneumonitis (or ILD) is mentioned in their respective SmPCs as an acknowledged side effect and which may have contributed to or caused the event. Rituximab, everolimus and/or bendamustine were reported as co-suspect drugs, while mesalazine and filgrastim were reported as concomitant drugs.<sup>2-6</sup> Details on when these drugs were started or stopped in relation to the events were not provided. The concomitant use of these drugs does not preclude a causal role for ibrutinib as a sole causal agent or it having an interactive or additive effect, but of course renders causality assessment from ibrutinib more difficult.

Apart from these 39 reported cases of pneumonitis there are also seven cases of the closely related condition ILD reported for ibrutinib in VigiBase. These cases are not described in detail in this signal review, but do show a similar pattern to the cases reported with pneumonitis.

Table 1 presents the cases which provide the best evidence of a causal relationship between ibrutinib and pneumonitis where investigation results, clinical course and lack of reference to antibacterial use support a diagnosis of non-infective pneumonitis.

### Literature and Labelling

Side effects of PKIs in general vary greatly depending on their precise mode of action with few or no side effects being common to them all. The

EU SmPC states the following regarding side effects of ibrutinib:

*"The safety profile is based on pooled data from 555 patients treated with IMBRUVICA in three phase 2 clinical studies and two randomised phase 3 studies and from post-marketing experience. [...] All patients in clinical studies received IMBRUVICA until disease progression or no longer tolerated.*

*The most commonly occurring adverse reactions (≥ 20%) were diarrhoea, musculoskeletal pain, upper respiratory tract infection, haemorrhage, bruising, rash, and nausea. The most common grade 3/4 adverse reactions (≥ 5%) were anaemia, neutropenia, pneumonia and thrombocytopenia."*<sup>1</sup>

Pneumonitis/ILD are acknowledged and labelled side effects for numerous PKIs although their detailed mode of action, molecular structure and their approved indication differ significantly and hence also their background disease and the spectrum of complications of the diseases. In VigiBase there are reports on pneumonitis/ILD for the vast majority of PKIs. There appears to be little firm knowledge on the pathophysiology of respiratory reactions in relation to PKIs in general.

Other notable side effects in several PKIs are electrolyte disturbances, hypertension, cardiotoxicity, and hepatotoxicity.

Ibrutinib is primarily metabolised by cytochrome P450 enzyme 3A4 and co-administration with subsequent interaction with strong or moderate CYP3A4 inhibitors may lead to higher toxicity and is hence discouraged in the SmPC. However, no such concomitant drug or dietary use was noted in any of the reported cases.

A publication by Mato et al. recently presents four cases of ibrutinib-induced pneumonitis in patients with a diagnosis of CLL. The patients, aged between 55 and 73 years, one woman and three men, had been diagnosed with CLL between 3 and 15 years prior to initiation of ibrutinib treatment. They had all had prior chemotherapy treatment, three of them with several courses. The time to onset of symptoms or hospitalization was between one and four months. The letter describes the authors' extensive evaluation, including trans-bronchial biopsies and infectious workup. Examples of biopsy sections are presented. CT scans prior, during and after the events are presented and show clear signs of the condition evolving during treatment. All patients were successfully treated with steroids and along with drug discontinuation the radiographic changes resolved, as did clinical symptoms. In one case a rechallenge was attempted with pneumonitis reoccurring. The authors hypothesize that "inhibiting signal



transduction pathways enhances expression of pro-inflammatory cytokines and the innate immune system. BTK also appears to serve as a critical mediator of lipopolysaccharide-induced dendritic cell maturation and macrophage polarization. Several

studies have reported an increase in alveolar infiltration of T helper 2 pro-inflammatory cytokines in BTK-deficient mice, resulting in airway inflammation".<sup>7</sup>

**Table 1.** Characteristics of case reports in Vigibase of pneumonitis in association with ibrutinib

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Ibrutinib daily dose	Reactions (MedDRA preferred terms)	Time to onset	Dechallenge, rechallenge, outcome	Indication, other relevant information
1	55/M	Valaciclovir, insulin (both C)	-	Pneumonitis	<7 months	Dechallenge positive, Rechallenge negative Outcome: recovered	CLL, physician report, non-smoker, heavily pre-treated, diagnosis confirmed via CT, treatment with steroids, assessed as related
2	73/M	Rituximab* (S)	420mg	Pneumonitis, diarrhea, anemia, acute kidney injury, pyrexia	1.5 months	Outcome: unknown	CLL, clinical trial report, patient presenting after 39 days with fatigue and fever, chest x-ray showing pneumonitis; antibiotics started, open biopsy confirmation of pneumonitis with negative cultures, acute respiratory failure with ICU treatment, assessed as related to ibrutinib or possibly to infection but not to rituximab or underlying disease
3	70/M	Levothyroxine, pantoprazole, ezetimibe, rosuvastatin, amlodipine, acetylsalicylic acid, metoprolol, Ω-3-acid (all C)	560mg	Pneumonitis, pneumonia, pleural effusion	5 months	Dechallenge positive	MCL, nurse report, diagnosis confirmed via CT and chest X-ray. treated with decreasing amounts of oxygen after withdrawal of drug. Superimposed pneumonia.
4	-/-	Rituximab*, bendamustine* (both S)	560mg	Pneumonitis, ARDS, rhinovirus infection	7 months	Fatal	Follicular lymphoma, study report ARDS during cycle 8, bronchoscopy culture positive for rhinovirus, grade 5 rhinovirus infection. Treated with broad spectrum antibiotics and high dose steroids
5	77/M	Warfarin, metformin, oxycodone, pioglitazone, nifedipine, furosemide (all C)	420mg	Pneumonitis, atrial fibrillation, congestive cardiac failure, swelling	3.5 months	Dechallenge positive	CLL, consumer/physician report, non-smoker, diagnosis of pneumonitis confirmed via CT, treated with antibiotics, causality assessed as related, patient restarted on idelalisib and rituximab.
6	66/F	10 concomitants none significant for pneumonitis	-	Pneumonitis, sepsis, death,	1.5 or possibly 6 months, (unclear data)	Fatal	CLL, nurse report, ex-smoker, two previous lines of therapy, death due to disease progression and reported reactions, sepsis assessed as not related to ibrutinib, no causality assessment for pneumonitis provided
7	78/M	10 concomitants none significant for pneumonitis	420mg 560mg- 280mg- 420mg- 280mg	Pulmonary fibrosis, pneumonitis, cough, fatigue, peripheral swelling, muscle spasms, arthralgia, myalgia, bone pain, nausea, pyrexia, nasopharyngitis	Approx. 3 months	Dechallenge positive Outcome: recovered	CLL, consumer/physician report, ex-smoker, differing information. History includes GERD, diabetes, arrhythmia, arthritis, heart disease, recurrent pneumonia, several previous lines of CLL treatment including rituximab, IVIG, cyclophosphamide, fludara. After one month of ibrutinib onset of musculoskeletal problems, fatigue. Dose decreased with positive effect. Dose re-increased with recurring fatigue, shortness of breath, cough and ultimately a pneumonitis diagnosis confirmed via chest X-ray. Dose decreased with some positive effect but ultimately ibrutinib withdrawal. Reinstating ibrutinib was discussed but no definite information.
8	82/M	-	-	Pneumonitis, respiratory failure	-	Dechallenge positive	CLL, literature report (Mahmoudi et al. <sup>9</sup> ) Presented hypoxic but without respiratory complaints after a fall with a scapula fracture. X-ray and CT scan findings suspicion of atypical infection from immunosuppression. Rapid deterioration and ICU treatment with mechanical ventilation. Absence of response to antibiotics, negative cultures, raised CRP, SR and low procalcitonin raises suspicion of inflammatory pneumonitis. Biopsy and BAL consistent with diagnosis. Rapid improvement on steroids after discontinuation of drug. Ibrutinib considered only identifiable agent.
9	57/F	-	420mg 280mg	Pneumonitis	9 months	Dechallenge positive, rechallenged at 280mg Outcome: recovered	CLL, physician report, treated on a named patient programme continuing after programme stopped, previous treatment including rituximab and bendamustine 4 years prior to event, history of bronchial asthma, pneumonitis detected by CT, rechallenge negative with reduced dose (six months follow up)
10	69/M	Filgrastim*, aciclovir, allopurinol, colecalciferol, chloramphenicol, erythropoietin, furosemide, prednisone, tranexamic acid (all C)	-	Pneumonitis	>4 months	Dechallenge positive	MCL, study report, diagnosis via signs, symptoms and typical X-ray findings. No data on previous lines of treatment. Treated with steroids, cyclophosphamide, oxygen. Recovered. Rechallenge was considered but was not performed as the patient developed AML. Timing of filgrastim not provided in detail.
11	72/M	-	420mg	Pneumonitis, sodium decreased	20 days	Dechallenge positive Outcome: recovering	CLL, pharmacist report, sparse information, treatment with posaconazole
12	72/M	Pantoprazole, tamsulosin, amlodipine, metoprolol, enoxaparin, aminophylline/quinine sulfate (all C)	420mg	Pneumonitis, pneumonia	2 weeks	Dechallenge positive, rechallenge negative (while on steroids) Outcome: recovering	MCL/CLL (MCL disease progression w leukemic course), physician study report, 2 previous lines of treatment, diagnosis confirmed via CT, BAL negative, recovered from pneumonia with antibiotics, recovered from pneumonitis with steroids and oxygen, study drug successfully rechallenged with concomitant steroid

\*Labelled for pneumonitis or related terms (such as interstitial lung disease).

A recent review by Shah on the subject of interstitial lung disease in TKIs provides a thorough overview of the disease with a focus on the TKIs for which this reaction is already labelled. Clinical features and laboratory findings are presented. Incidence data provided is discussed and refers to a large extent to TKIs used for non-small cell lung cancer and to Japanese patients, with their apparently different and higher susceptibility for the reaction. Onset of the reaction in TKIs based on clinical trials and post authorization studies vary heavily between different TKIs from days to many months (and usually within a year) with more severe reactions usually appearing earlier in the course. A discussion of the management of the reaction includes common practices for ILD namely discontinuation of the culprit, steroids, supportive care and when relevant antibiotics.<sup>8</sup>

### Discussion and Conclusion

There are 21 PKIs for which pneumonitis has been disproportionately reported in VigiBase. The vast majority of them have pneumonitis, or less often, ILD present in their labelling. Ibrutinib, with 39 reports on pneumonitis and 7 on ILD in VigiBase is one of the few exceptions to this.

The 39 cases of pneumonitis reported show a reasonably consistent pattern and history to support a causal relationship between ibrutinib and pneumonitis. The temporal association in the majority of cases supports a causal relationship being similar to the natural history of pneumonitis. The majority of cases were reported by the physician diagnosing and treating the event, but the level of detail in the description of diagnostic methods used is not high. A positive dechallenge and outcome is described in many of the cases, in some also recording steroid treatment. Antibiotic treatment is often mentioned which would be expected considering that when diagnosing pneumonitis symptoms of respiratory infections overlap with those of pneumonitis and serious infectious processes always have to be ruled out and treated. No case of certain positive rechallenge is described in the spontaneously reported cases.

In some cases there are other explanations or evident confounders present; other suspected or concomitant drugs; in some cases, several previous lines of treatment for the disease, and in at least one case prior radiotherapy to the chest could be possible predisposing factors of the pneumonitis. The underlying disease may have contributed in only few of the cases reported. Likewise, few of the reported cases describe previous potentially predisposing respiratory disease; one patient did have a history of recurrent pneumonitis. In four of the cases a negative rechallenge at the same or lower dose is described. The reports from Italy pose a specific challenge in that due to translation and nomenclature issues we cannot rule out the possibility that among them may be cases of pneumonia rather than pneumonitis.

The publication by Mato et al. on four further thoroughly evaluated and described cases with similar histories strongly supports the signal.

In summary, with a clinical suspicion and a pattern in a majority of reported cases consistent with drug induced pneumonitis and a recent publication describing a series of clinically detailed described cases with a strong suspicion of causality, with the vast majority of drugs in the protein kinase inhibiting class having pneumonitis or interstitial lung disease as an acknowledged side effect in their labelling; the signal of pneumonitis induced by ibrutinib merits further investigation to assess the need for possible risk minimising activities by relevant stakeholders.

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## Pregabalin and visual colour distortions

*Dr Linda Härmark, the Netherlands Pharmacovigilance Centre Lareb*

### Summary

Twenty-five reports in the WHO global database of individual case safety reports, VigiBase, describe a relationship between the drug pregabalin and changes in colour vision. Based on these reports, it is recommended to add changes in colour vision to the product information leaflet of pregabalin.

Poor or deficient colour vision, often referred to as colour blindness, is an inability to distinguish between certain colours, while still seeing colour. Colour blindness can be inherited (most common) or it can be caused by diseases or drugs. Pregabalin (Lyrica®) is a drug that can be used for the treatment of pain due to nerve injury, fibromyalgia, epilepsy and anxiety disorders.

On the basis of the 25 reports in VigiBase that were highlighted in the joint UMC/Lareb signal detection sprint that took place in October 2016, it seems that the time to onset is quick, the changes in colour vision seem to occur within hours to days after starting the drug. This adverse reaction also seems to be reversible; in seven cases the patients regained normal colour vision after stopping pregabalin.

Although changes in colour vision can have other causes, the relationship with pregabalin is strengthened by the fact that changes in colour vision is a known adverse reaction of other drugs (vigabatrin and tiagabine) which exert their effects in a similar way as pregabalin.

### Introduction

Pregabalin has been approved for the European Union (EU) and United States (US) markets since 2004. It is indicated for the treatment of neuropathic pain, posttherapeutic neuralgia, diabetic peripheral neuropathy, fibromyalgia, epilepsy and for generalised anxiety disorder.<sup>1,2</sup> Pregabalin is a  $\gamma$ -aminobutyric acid (GABA) analogue and exerts its effects by binding to the  $\alpha 2 - \delta$  subunit of voltage gated calcium channels, leading to a decreased synaptic release of neurotransmitters.<sup>3</sup>

Poor or deficient colour vision, often referred to as colour blindness, is an inability to see the difference between certain colours, while still seeing colour. Most people with this condition cannot distinguish between certain shades of red and green. Less

commonly, people with poor colour vision cannot distinguish between shades of blue and yellow. Poor colour vision can be inherited (most common) or be acquired. Poor colour vision can be caused by diseases such as sickle cell anaemia, diabetes, macular degeneration, Alzheimer's disease, glaucoma, Parkinson's disease, chronic alcoholism and leukaemia. Certain medications such as antibiotics, barbiturates, anti-tuberculosis drugs, high blood pressure medications and several medications to treat nervous disorders may also cause colour blindness. For people without poor or deficient colour vision, the ability to see colours deteriorates slowly with age.<sup>4,5</sup>

Chromatopsia is a visual defect in which coloured objects appear unnaturally coloured, and colourless objects appear tinged with colour. Chromatopsia may be caused by drugs, disturbance of the optic centres, cataract extraction or dazzling light.<sup>6</sup>

Pregabalin is associated with a number of adverse drug reactions (ADRs) affecting the eye, such as blurred vision, diplopia, peripheral vision loss, visual disturbance, eye swelling, visual field defect, reduced visual acuity, eye pain, asthenopia, photopsia, dry eyes, increased lacrimation, eye irritation, vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus and visual brightness.<sup>1</sup> However, visual colour distortions such as colour blindness and chromatopsia, have not been described.

### Reports in VigiBase

This drug-ADR combination was identified in a signal detection screening with focus on patient reports in VigiBase, the WHO global database of individual case safety reports. In total, eight reports were identified using the MedDRA preferred term (PT) 'colour blindness', and 13 reports using the MedDRA PT 'chromatopsia'. The reports are presented in Table 1. The presentation of reported ADRs in the table has been restricted to those concerning the eye, and other ADRs that were reported have been omitted.

**Table 1.** Characteristics of case reports in VigiBase of colour blindness and chromatopsia in association with pregabalin. ADRs are restricted to those related to the eyes.

Case	Reporter	Sex/ Age	Suspected (S), Interacting (I) or concomitant (C) drugs	Indication	Daily dose	Reactions (MedDRA preferred terms related to the eye)	Time to onset	Action taken with the drug, Outcome
1	Consumer	F/ Adult	Pregabalin, methylprednisolone, paracetamol/tramadol (all S)	Neuralgia	75 mg once daily	Eyes swollen, flashing vision, burning sensation in face, vision abnormal, colour blindness,	Within a day to 3 days	Drug withdrawn Recovered
2	Consumer	F/ 59	Pregabalin (S) Morphine, paracetamol/ oxycodone (both C)	Fibromyalgia	75 mg twice daily	Cataract, blindness, impaired driving ability, visual impairment, foreign body in eye, colour blindness, visual acuity reduced	-	Dose not changed Cataract, blindness, colour blindness - recovered Impaired driving ability, foreign body in eye, backpain - outcome not applicable Visual impairment and visual acuity - outcome unknown
3	Consumer	M/-	Prednisone, paracetamol (Both S) Pregabalin, amitriptyline (both I)	Nerve injury, limb injury	-	Astigmatism, transient blindness, colour blindness, eye disorder, eye irritation, vision blurred, visual impairment	-	Drug withdrawn Astigmatism, colour blindness and visual impairment, not recovered Outcome unknown for all other events
4	Physician	F/-	Pregabalin (S), Hydrocodone, folic acid, alprazolam, modafinil, paracetamol/hydrocodone bitartrate (all C)	Fibromyalgia	-	Colour blindness, scotoma, vision blurred	-	Dose reduced Recovered from vision blurred Outcome unknown for the other events
5*	Consumer	F/-	Pregabalin, varenicline (both S) Sodium chloride, duloxetine, benzonatate, tramadol, methylphenidate, diazepam, salbutamol, fluticasone/salmeterol (all C)	Fibromyalgia	50 mg three times daily	Colour blindness, diplopia, impaired driving ability, ophthalmological examination abnormal	-	Dose not changed Outcome unknown or not applicable for all events
6	Unknown	F/44	Pregabalin (S)	Nervousness, pain	50 mg three times daily	Colour blindness, eye pain, intraocular pressure increased, visual disturbance, visual field defect	-	Action taken with the drug is not reported Outcome unknown
7	Physician	F/37	Pregabalin (S) Lorazepam, esomeprazole, levothyroxine (all C)	Generalized anxiety disorder	50 mg once daily	Vision blurred, tunnel vision, defective colour vision	1 hour	Dose not changed Not recovered
8	Physician	M/63	Pregabalin (S) Ramipril, tramadol (both C)	Polyneuropathy	-	Peripheral vision defective, blurred vision, defective colour vision	"Days"	Drug withdrawn Recovered Rechallenge was performed - no recurrence of events
9	Consumer	F/59	Pregabalin (S) Paracetamol/oxycodone, prednisone, ibuprofen (all C)	-	75 mg three times daily	Diplopia, vision blurred, chromatopsia	-	Action taken with the drug is not reported Outcome unknown
10	Consumer	F/31	Pregabalin (S) Patient used 30 concomitant drugs	Fibromyalgia	150-200 mg twice daily	Visual impairment, ocular discomfort, migraine, photophobia, face injury, impaired driving ability, activities of daily living impaired, vision blurred,	-	Dose reduced Outcome unknown

# SIGNAL

Case	Reporter	Sex/ Age	Suspected (S) or concomitant (C) drugs	Indication	Daily dose	Reactions (MedDRA preferred terms related to the eye)	Time to onset	Action taken with the drug, Outcome
11	Pharmacist	M/78	Pregabalin (S) Acetylsalicylic acid, atenolol, cetirizine, clopidogrel, isosorbide, lansoprazole, nicorandil, perindopril, simvastatin (all C)	Post herpetic neuralgia	75 mg twice daily	Vision colour tinged, sleepy	Within a day	Drug withdrawn Recovered
12	Consumer	F/65	Pregabalin (S) Baclofen, tizanidine, celecoxib (all C)	Neuralgia	50 mg three times daily	Chromatopsia, dizziness, somnolence, vision blurred, fatigue	-	Action taken with the drug is not reported Outcome unknown
13	Other HCP	F/-	Pregabalin (S) Morphine, levothyroxine, hydrochlorothiazide, vitamin D, sertraline, tocopherol, zolendronic acid, cyanocobalamin, calcium (all C)	Fibromyalgia	100 mg three times daily	Impaired driving ability, chromatopsia, visual acuity reduced, vision blurred	-	Dose reduced Not recovered
14	Other HCP	M/-	Pregabalin (S)	-	-	Chromatopsia, visual acuity reduced, visual impairment	-	Action taken with the drug is not reported Outcome unknown
15	Physician	M/75	Pregabalin (S), Telmisartan, tamsulosin, omeprazole, acetylsalicylic acid, torasemide (all C)	Pain NOS	75 mg twice daily	Vision abnormal, eye pain, chromatopsia	For vision abnormal a day, for the other events a few days	Drug withdrawn Recovered
16	Other HCP	F/-	Pregabalin (S), Ibandronnic acid, methylprogesterone acetate/conjugated estrogens, oxycodone, levothyroxine, retinol, calcium, paracetamol/ hydrocodone (all C)	Not reported	75 mg three times daily	Activities of daily living impaired, chromatopsia, visual acuity reduced, visual field defect, visual impairment	Unknown, for visual impairment 7 months	Drug withdrawn Chromatopsia recovered Outcome of Activities of daily living impaired - unknown Visual acuity reduced, visual field defect and visual impairment - not recovered
17	Pharmacist	F/44	Pregabalin (S)	Diabetic neuropathy	-	Chromatopsia, photophobia, tunnel vision	-	Drug withdrawn Recovered
18	Consumer	M/-	Pregabalin (S) Hydrocodone, oxycodone, olmesartan, diltiazem, fluticasone/salmeterol, tiotropium (all C)	Back injury	50 mg three times daily	Astenopia, chromatopsia, vision blurred	2 months	Drug withdrawn Not recovered
19**	Other HCP	M/59	Pregabalin (S), modafinil, metformin, glimepiride (all C)	Diabetic nephropathy	-	Chromatopsia	-	Drug withdrawn Recovered
20	Physician	F/-	Pregabalin (S)	Ill-defined disorder	-	Chromatopsia	-	Drug withdrawn Outcome unknown Rechallenge was performed - outcome unknown
21	Unknown	M/51	Pregabalin (S), Paracetamol/hydrocodone, carisoprodol, zolpidem (all C)	Neck pain	-	Chromatopsia	-	Drug withdrawn Outcome unknown Rechallenge was performed - outcome unknown

NOS= Not otherwise specified. \*Case 5; In this case CT abnormal, convulsion, EEG abnormal, loss of consciousness, pineal neoplasm and pituitary tumour were also reported. It is more likely that the reported symptoms concerning the eye were caused by the tumour rather than by pregabalin. \*\*Case 19, the author of this signal suspected that the indication for use should be diabetic neuropathy.

In case 1, the patient had previously used pregabalin at high doses to treat her trigeminal neuralgia and experienced dizziness, somnolence and intense lethargy which were resolved after discontinuation of pregabalin. No allergy was experienced at that time. The symptoms started with a burning face, and the morning after she had a tendency to vomit, facial rash and swelling of the eyes. Paracetamol/tramadol was withdrawn, since this was the drug she had not previously used. The next day the rash had expanded and she experienced pruritus, she had flashes in her eyes, and intense lights and she could not distinguish items (also reporting that everything looked square). In addition, at an unspecified date the patient could not recognize colours.

In case 7, one hour after the first dose the patient developed tunnel vision, impaired colour vision, blurred vision and difficulties in reading. The patient had no medical history of retinal degeneration, ophthalmological or neurological diseases and no history of eye diseases.

In case 8, the patient noticed a gradually worsening visual disorder with blurred vision over a few days, peripheral vision impairment, and loss of perception of colour after the dose was increased from 25 mg twice daily (treatment duration unknown) to 75 mg twice daily. Pregabalin was discontinued and the patient recovered. The patient's medical history included diabetes mellitus, hypertension, peripheral arterial occlusive disease, strabismus and alcohol use.

In three cases (3, 13 and 18) the patient had not recovered at the time of reporting, even though the drug had been withdrawn or the dose had been reduced. It is possible that the report was submitted before the patient had the opportunity to recover. Other explanations might be that in some cases the colour vision distortion is not reversible or that the colour vision distortion in these patients were not caused by pregabalin and therefore did not improve when withdrawing or reducing the dose of the drug.

### Literature and Labelling

Colour vision distortions such as colour blindness and chromatopsia are not labelled in the EU summary of product characteristics or Drugs.com.<sup>1,2</sup> These ADRs are also not mentioned in the literature<sup>7,8</sup> and a PubMed search using the terms "Colour Vision Defects"[Mesh] AND "Pregabalin"[Mesh] returned no hits. However, colour vision disturbances have been documented with anti-epileptic drugs; primarily, but not exclusively, in anti-epileptic drugs that enhance GABA transmission.

In a study, the effects of a single oral dose of vigabatrin (VGB) and carbamazepine (CBZ) on visual function in normal healthy volunteers was investigated. Volunteers were randomly assigned to three groups according to a single-blind, placebo-

controlled design. All subjects underwent colour visual evoked potential tests and colour perimetry at baseline and after receiving placebo, VGB (2000 mg) or CBZ (400 mg). Whereas CBZ induced a mild overall impairment of the chromatic and achromatic systems, VGB induced a selective blue impairment. The differential changes the two antiepileptic drugs induced in visual tests presumably depended on their different mechanisms of action. The selective blue impairment in colour visual tests in VGB-treated healthy subjects is consistent with gamma-aminobutyric acid GABA-ergic inhibition also at retinal level.<sup>9</sup>

A further study investigated colour vision in patients treated with VGB or CBZ monotherapy. There were 32 epilepsy patients treated with VGB monotherapy, 18 patients treated with CBZ monotherapy, and 47 age-matched healthy controls examined. Abnormal colour perception was found in 32% of the epilepsy patients treated with VGB monotherapy and 28% of the epilepsy patients treated with CBZ monotherapy.<sup>10</sup>

In another study, the effects of the GABA-ergic antiepileptic drug (AED), tiagabine, on colour vision and contrast sensitivity was investigated. Twenty newly-diagnosed patients with partial epilepsy (aged 19-72 years), receiving tiagabine as their initial monotherapy for 5-41 months were examined. Three patients were excluded from the colour vision evaluation for congenital red-green colour vision defects. Seven out of 17 patients (41%) had acquired colour vision deficit. This study suggests that AED therapy with tiagabine, as with other established and newer AEDs may interfere with colour perception.<sup>11</sup>

In the studies described above, it seems that the GABA-ergic properties of VGB and tiagabine contribute to the colour vision deficiency. VGB is an irreversible inhibitor of GABA-transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This inhibition causes increased levels of GABA in the central nervous system. Tiagabine is thought to inhibit GABA uptake into presynaptic neurons, thereby providing more GABA available for binding to receptors on postsynaptic cells. This enhances the activity of GABA, the major inhibitory neurotransmitter in the central nervous system. It is possible that the colour vision distortion seen in patients using pregabalin can be explained by the same mechanism. Pregabalin is a GABA analogue and thereby enhancing GABA activity just as VGB and tiagabine.<sup>12</sup>

## Discussion and Conclusion

This signal presents a case series of 25 reports concerning pregabalin and colour vision distortions. When information about the latency period is present, it seems that the symptoms develop quite quickly within hours to days after the start of the drug. In seven cases there is a positive dechallenge, indicating that this adverse drug reaction is reversible when the drug is withdrawn. Colour vision distortions can also have other causes, such as sickle cell anaemia, diabetes, macular degeneration, Alzheimer's disease, glaucoma, Parkinson's disease, chronic alcoholism and leukaemia. Pregabalin is indicated for use in diabetic peripheral neuropathy, and in such cases it is possible that the diabetes could be the cause of the colour vision distortion. However, in the case series only one case explicitly states that the indication was diabetic peripheral neuropathy, and in this case the patient recovered after withdrawal of the drug, hence eliminating confounding by indication. In case 5, it is more likely that the patient's tumour was the cause of the colour vision distortion than the drug.

In the literature, colour vision distortions have been described with the use of VGB and tiagabine. It is believed that this effect is mediated by the GABA-ergic effects of these drugs on the retina. Pregabalin, which is a GABA analogue, could probably cause colour vision distortions through the same mechanisms. With this case series and a mechanism which can explain how pregabalin can cause colour vision distortion, we believe that this association is a signal and that the term colour vision should be included in the label.

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## SGLT-2 inhibitors and genital pruritus

A non-serious event with the potential for noncompliance and/or discontinuation

*Dr Rebecca E Chandler, Uppsala Monitoring Centre*

### Summary

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are members of a relatively new class of oral antidiabetic agents which are used in the treatment of type 2 diabetes mellitus as monotherapy or in combination with other agents. Itching in the genital area is a common non-serious adverse

reaction for these types of drugs which was known at the time of approval. A joint UMC/Lareb signal detection sprint performed in October 2016, highlighted reports from patients that were retrieved from VigiBase, the WHO global database of individual case safety reports, which revealed that often patients

stop taking these medications because of this adverse event.

*A 71 year old female with a history of type 2 diabetes and hypertension was initiated on empagliflozin. The patient was treated for cystitis approximately one month after starting therapy. Also, the patient experienced non-serious events of thrush, burning in the urogenital area, redness in the urogenital area, blistering in the urogenital area and hypoglycaemia. In the course of five days the itching increased up to intolerability. Therapy for the event of cystitis was antibiotics and antifungal cream; therapy of the symptoms in the urogenital area included unspecified ointments without success and a mild-cortisone containing ointment which helped slightly. Empagliflozin was discontinued.*

*A 60 year old female experienced severe itching, soreness, and reddening of the genital area and an inability to sit while on therapy with dapagliflozin. The patient was diagnosed with candidal mycosis and treated with antifungal cream. The cream did not bring improvement and the patient discontinued dapagliflozin "on her own" in response to the events.*

## Introduction

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are members of a relatively new class of oral antidiabetic agents. Three medicines in this class, dapagliflozin, canagliflozin and empagliflozin, are currently marketed for use in the treatment of type 2 diabetes mellitus as monotherapy or in combination with other agents.

SGLT-2i work by inhibiting glucose reabsorption in the kidney and thereby promoting urinary excretion of glucose. Studies have revealed that SGLT-2i have beneficial effects on blood glucose levels, but also they reduce blood pressure and induce weight loss. Given that the action of these agents is independent of both insulin secretion and insulin action, another benefit of these agents is a lower risk of hypoglycaemia.<sup>1</sup>

Given their mechanism of action, one of the major safety concerns for the SGLT-2i is an increased risk of genital infections caused by high levels of glucose in the urine. This safety concern is common enough that it was observed in clinical trials and has been fairly well characterised. Genital infections are largely fungal in nature, manifesting as mycotic vulvovaginitis in females and mycotic balanitis in males. Such infections have been estimated to affect 5-10% of patients using SGLT-2i and are more common in premenopausal women, patients with a history of genital infections, and obese patients. There was no evidence of a relationship between the incidence of genital infections and the amount of glycosuria observed in the clinical trials. Furthermore, rates of infections are highest in the first few months of treatment.<sup>2-4</sup>

## Reports in VigiBase

During a joint UMC/Lareb signal detection sprint with a focus on patient reports, a total of 99 individual case safety reports which included the MedDRA preferred term (PT) 'pruritus genital' for dapagliflozin, canagliflozin and empagliflozin were identified in VigiBase, the WHO global database of individual case safety reports as of 6 November 2016.

Forty-eight reports of pruritus genital (48.5%) have been received for dapagliflozin, 31 (31.3%) for canagliflozin and 20 (20.2%) for empagliflozin.

67.7% of the reports have been described events in females, 28.3% of the reports for males.

40.4% of the reports originated from the Americas, 36.4% from Europe, and 23.2% from Asia.

The most commonly co-reported MedDRA PT were genital burning sensation (9.1%), pollakiuria (7.1%) and dysuria (5.1%).

Twenty-three of the reports were received from consumers or non-health professionals (eight of which were classified as "serious") and 25 were received from physicians (none of which were classified as "serious"). Furthermore, fifty-four (54.5%) of the reports documented that the drug was discontinued secondary to the reported adverse drug reactions.

## Literature and Labelling

The summary of product characteristics for each of these products notes that most genital infections were mild to moderate and only rarely resulted in discontinuation. The patient information leaflet notes only that genital infections are common to very common and manifest with irritation, itching, unusual discharge or odour. There is no information provided to the patient to seek medical consultation for treatment of these infections.

## Discussion and Conclusion

The aim of communication is to highlight that some events can be characterised as non-serious in the clinical trial setting but may manifest in the post marketing period as severe events which have a large enough impact on the quality of life for the patient that discontinuing the medication is necessary.

Additionally, more guidance by drug developers or regulators on how to manage these effects may be necessary to ensure that patients who receive benefit from taking the medications are able to remain compliant with them.



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# CAVEAT DOCUMENT

## ***Accompanying statement to data released from VigiBase®, the WHO international database of suspected adverse drug reactions***

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring (PIDM). The information is stored in VigiBase®, the WHO international database of suspected adverse drug reactions (ADRs). It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase® make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

If in doubt or in need of help for interpretation of country specific data, UMC recommends to contact the concerned NC before using the data.

**For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.**

### **Confidential data**

According to WHO policy and UMC Guidelines, ADR reports sent from the WHO PIDM member countries to VigiBase® are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase® Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from UMC must include a statement:

- (i) regarding the source of the information
- (ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
- (iii) that the information does not represent the opinion of the World Health Organization.

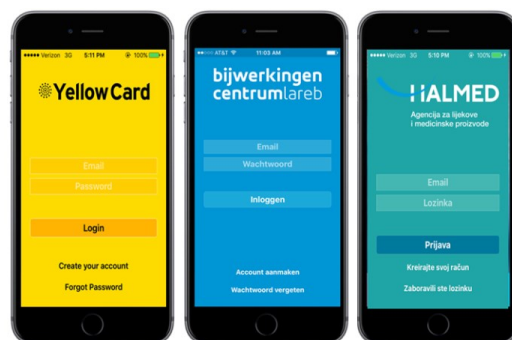
**Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase®.**

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

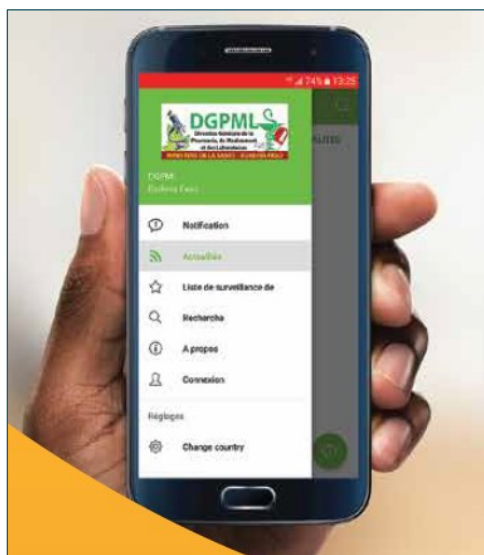
## Pilot Mobile 'APP' for reporting suspected adverse drug reactions launched in Burkina Faso and Zambia

As we are evolving towards a paperless world, it is not a surprise that there is an increase in demand for electronic adverse drug reaction (ADR) reporting options. Many countries are utilising electronic reporting forms via a web-link that can be obtained on a computer screen. The link is often located on the website of the national pharmacovigilance centre and requires internet access in order to report an ADR. Although the use of electronic reporting via a website is thought to increase the frequency and timeliness of reporting, the requirement of a computer and internet access may limit its use, particularly in countries and areas where there is poor or intermittent internet access. Recent technological advances have led to the development of mobile apps for reporting ADRs, many of which allow reports to be made offline with the possibility of sending the report later when the user is online and internet access is available.

Croatia, the Netherlands and UK have rolled out a mobile 'app' that was developed as part of the "Web-Recognising Adverse Drug Reactions (WEB-RADR)" project. This project is supported by the European Commission's Innovative Medicines Initiative, and explores the volume, breadth and quality of social media data, and consequently, where they may add value from a pharmacovigilance perspective. One of the work packages of this initiative is dedicated to developing a mobile app for reporting ADRs. The app is the same in all three countries, except that it is translated and branded for different national settings. An additional feature of this app is that it promotes two-way communication by providing feedback to the reporter after a report has been submitted. Such feedback can range from a confirmation that the report was received, to an overview of how often a type of ADR has been reported and what has been done with the report that was submitted.



The concept of a WHO "white app" was announced at the 39th Annual Meeting of Representatives of the National Pharmacovigilance Centres Participating in the WHO Programme for International Drug Monitoring (PIDM), in Muscat Oman, November 2016 (1). The notion of the 'white app' envisages making the WEB-RADR app available to other non EU countries in the WHO PIDM. It is non-branded and can be built-upon by the country interested in using the app and adapted to the national context. Drug lists and MedDRA\* terms can be incorporated as drop down lists, in addition to free text. The app will be made available to other countries through a stepwise approach starting with a pilot phase in one French and one English speaking country.



The WEB-RADR team in collaboration with WHO worked with representatives from Burkina Faso and Zambia to nationalise the app in both countries. After preliminary testing, the app went live on 8 May 2017. Both countries are planning a widespread awareness campaign, involving leaflets, interviews on the radio, television and an official launch ceremony. WHO plans to use the experiences from the pilot countries to draw lessons learnt as part of the initial steps towards making the app available for all.

1. World Health Organization. The 39th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. The WHO Pharmaceuticals Newsletter. 2016(6):26-7.

\* Medical Dictionary for Regulatory Activities, developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to provide single standardised international medical terminology to be used for regulatory communication and evaluation of data pertaining to medicinal products for human use.

## Introducing a New Member in the WHO Programme for International Drug Monitoring (WHO PIDM): Paraguay



El Dpto. de Farmacovigilancia fue creado e incorporado al organigrama de la Dirección Nacional de Vigilancia Sanitaria dependiente del Ministerio de Salud Pública y Bienestar Social mediante Resolución Ministerial S.G. N° 314 en el año 2013.

A la fecha este Departamento se encuentra enmarcado dentro del proceso de fortalecimiento institucional e interactuando con otras dependencias del Ministerio de Salud, especialmente con los programas de lucha contra el SIDA (PRONASIDA) y la Tuberculosis (PNCT).

En el último año se han incorporado nuevos elementos al marco regulatorio especialmente con miras a la implementación de las Buenas Prácticas de Farmacovigilancia y actualmente se encuentra abocado a la creación de una red de hospitales centinela.

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The Department of Pharmacovigilance was established under the National Agency of Health Surveillance, Ministry of Public Health and Social Welfare after the Ministerial Resolution S.G. No. 314 was issued in 2013.

To date, this Department is involved in strengthening pharmacovigilance practices and regularly interacts with other units of the Ministry of Health, in particular HIV (PRONOSIDA) and TB (PNCT) public health programmes.

Since last year, new components have been added to the regulatory framework, and there is a focus on implementing Good Pharmacovigilance Practices, and forming a pharmacovigilance network in sentinel hospitals.