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# WHO Pharmaceuticals NEWSLETTER

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***WHO Vision for Medicines Safety***
***No country left behind:***
***worldwide pharmacovigilance***
***for safer medicines, safer patients***

*The aim of the Newsletter is to disseminate regulatory information on the safety of pharmaceutical products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.*

*The information is produced in the form of résumés in English, full texts of which may be obtained on request from:*

***Safety and Vigilance: Medicines,***

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

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from the WHO global database of individual case safety reports, VigiBase.

In addition, this edition of the Newsletter includes articles on COVID-19 vaccines: Safety Surveillance Manual and the Vaccine Safety Net (VSN) Virtual Meeting.

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## Regulatory Matters



## Safety of medicines



## Signal



## Feature

## Asparaginase

### Risk of sepsis

**Republic of Korea**. The Ministry of Food and Drug Safety (MFDS) has updated the drug label for asparaginase products to include the risk of sepsis.

Asparaginase is a bacterial enzyme used in the treatment of acute lymphoblastic leukemia.

During the evaluation process of serious adverse event (SAE) reports, the Korea institute of Drug Safety and Risk Management (KIDS) reviewed one fatal SAE report of sepsis in a patient who received asparaginase-containing lymphoma treatment regimen. The signal detected from the SAE report was re-assessed through routine signal analysis process.

At the time of review, the KIDS had received three domestic and 76 foreign reports of sepsis with asparaginase through the Korean adverse event reporting system since 1989. Data mining results of the reports within the database identified a statistical association between asparaginase and sepsis. Case evaluation was performed on these reports, in which a causal association could not be excluded.

This recommendation announced by the MFDS was based on the results of SAE review system and signal analysis and evaluation procedure at KIDS.

Health-care professionals should be reminded of the possible hematologic toxicities and myelosuppressive effects of asparaginase-containing chemotherapy regimen and are advised to monitor for any signs of serious infections during use of this drug.

***Reference:***
Based on the communication from MFDS and KIDS, Republic of Korea, November 2020

## Benzodiazepine

### Boxed warning updated to improve safe use

**USA**. The US Food and Drug Administration (FDA) has announced that it is requiring that the Boxed Warnings of benzodiazepine containing products are updated to include information on the risk of abuse, misuse, addiction, physical dependence and withdrawal reactions.

Benzodiazepines are indicated to treat generalized anxiety disorders, insomnia, seizures, social phobia and panic disorders.

Health-care professionals prescribing a benzodiazepine should consider the patient's condition, any concomitant medicines and assess the risk of abuse, misuse and addiction.

Also health-care professionals should limit the dosage and duration of the prescribed benzodiazepine to the minimum needed to achieve the desired clinical effect. Upon discontinuation dosage should be reduced gradually to reduce the risk of acute withdrawal reactions.

Precautions should be taken when benzodiazepines are used in combination with opioid addiction medications.

***Reference:***
MedWatch, US FDA, 23 September 2020 *(*www.fda.gov*)*

*(See also WHO Pharmaceuticals Newsletter No.3, 2020: Risk of potentially fatal respiratory depression in UK, No.5, 2016: Serious risk of slowed or breathing difficulties and deaths in US)*

## Cytarabine

### Risk of cytarabine syndrome

**Japan.** The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for cytarabine (Cylocide®) should be revised to include cytarabine syndrome as an adverse drug reaction.

Cytarabine is indicated to treat acute leukaemia, gastrointestinal carcinoma, lung cancer, breast cancer, female genital cancer and bladder tumour.

A total of two cases of cytarabine syndrome in patients treated with cytarabine have been reported in Japan during the previous three years, for which a causal relationship between the drug and event was reasonably possible. To date, no patient mortalities have been reported.

Symptoms of cytarabine syndrome include pyrexia, muscle pain, bone pain and malaise. Patients should be carefully monitored, and if any of these symptoms occur, appropriate measures should be taken such as administration of a corticosteroid.

The MHLW and PMDA have concluded that a revision of the package insert was necessary.

***Reference:***
Revision of Precautions, MHLW/PMDA, 6 October 2020 *(*www.pmda.go.jp/english/*)*

## Dolutegravir

### Updated advice on increased risk of neural tube defects

**United Kingdom.** The Medicines and Healthcare products Regulatory Agency (MHRA) has announced that updated safety recommendations have been issued as part of the European review evaluating cases of neural tube defects in babies born to mothers who became pregnant while taking the HIV medicine dolutegravir (Tivicay®, Triumeq® and Juluca®).

Dolutegravir is an integrase

inhibitor indicated in combination with other anti-retroviral medicinal products for the treatment of HIV in adult, adolescents, and children older than six years.

In June 2018, preliminary results from an observational study suggested an increased risk of neural tube defects in infants born to women who took dolutegravir at the time of conception. While a review of this signal was ongoing, the MHRA asked health-care professionals not to prescribe dolutegravir to women who are trying to become pregnant.

Evidence in the latest review shows a smaller increased risk than previously thought, almost comparable to other HIV drugs.

Health-care professionals should counsel women of childbearing potential about the possible risk of neural tube defects with dolutegravir, including consideration of effective contraceptive measures. Also, if a pregnancy is confirmed in the first trimester while a patient is on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patients.

***Reference:***
Drug Safety Update, MHRA, 22 October 2020 *(www.gov.uk/mhra)*

*(See also Full List of WHO Medical Product Alerts, WHO, October 2018 (http://www.who.int/medicines/publications/drugalerts/DTG_followon_may2018.pdf?ua=1) and WHO Pharmaceuticals Newsletter No.6, 2018: Risk of neural tube defects in Europe)*

## Erythromycin

### Risk of cardiovascular event and infantile hypertrophic pyloric stenosis (IHPS)

**Ireland.** The Health Products Regulatory Authority (HPRA) has announced that the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for erythromycin-containing medicines have been updated to reflect current knowledge of the risks of cardiovascular event and, infantile hypertrophic pyloric stenosis (IHPS).

Erythromycin is a macrolide antibiotic known to be associated with a risk of QT-prolongation and cardiac arrhythmia.

The European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) conducted an assessment of erythromycin-containing medicines and considered data from observational studies that identified a rare, short-term risk of cardiovascular events associated with macrolides including erythromycin. Based on this data, the PRAC recommended that the risk of cardiovascular events should be balanced with known treatment benefits when prescribing erythromycin-containing medicines, particularly in patients at high risk of cardiovascular events.

Also, results of the review supported a potential association between exposure of erythromycin in infants and the risk of IHPS.

Erythromycin should not be administered to patients with a history of QT-prolongation or ventricular cardiac arrhythmia or electrolyte disturbances.

***Reference:***
Drug Safety Newsletter, HPRA, September 2020 *(www.hpra.ie)*

## Fentanyl (transdermal patch)

### Contraindication in opioid-naive patients recommended

**United Kingdom.** The MHRA has announced that the Commission on Human Medicines (CHM) has recommended that fentanyl transdermal patches are contraindicated in opioid-naive patients, due to the risk of respiratory depression.

Fentanyl is a potent opioid analgesic.

The CHM convened an expert working group to examine the benefits and risks of opioids in the relief of non-cancer pain.

Up to May 2020, the MHRA has received 13 cases of respiratory depression following use of fentanyl in opioid-naive patients.

Because of the risk of respiratory depression, the use of fentanyl patches in non-cancer patients should be limited to only those who have previously tolerated opioids.

The initial dose of fentanyl should be based on a patient's opioid history.

***Reference:***
Drug Safety Update, MHRA, 23 September 2020 *(www.gov.uk/mhra)*

*(See also WHO Pharmaceuticals Newsletter No.6, 2018; Life-threatening and fatal opioid toxicity from accidental exposure in UK; No.4, 2014: Reminder of potential life-threatening harm from accidental exposure, particularly in children)*

## Flucytosine

### Contraindication in patients with dihydropyrimidine dehydrogenase (DPD) deficiency

**United Kingdom.** The MHRA has announced that flucytosine (Ancotil®) is contraindicated for use in patients with complete and partial dihydropyrimidine dehydrogenase (DPD) deficiency, due to the risk of life-threatening and severe toxicity.

Flucytosine is a prodrug of 5-fluorouracil used to treat systemic yeast and fungal infections.

DPD activity is rate limiting in the catabolism of 5-fluorouracil. Patients with DPD deficiency are therefore at increased risk of toxicity, including stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity.

In order to avoid a delay in starting antimycotic therapy, testing for DPD deficiency is not required before treatment with flucytosine. However, determination of DPD activity should be considered when there is a confirmed or suspected drug toxicity. In case of suspected drug toxicity, discontinuation of the treatment with flucytosine should be considered.

***Reference:***
Drug Safety Update, MHRA, 22 October 2020 *(www.gov.uk/mhra)*

## 5-Fluorouracil (intravenous), capecitabine, tegafur

### Dihydropyrimidine dehydrogenase (DPD) deficiency testing recommended before initiation

**United Kingdom.** The MHRA has announced that the product information (SmPC and Patient Information Leaflets (PIL)) for 5-fluorouracil, capecitabine and tegafur will be updated to include information on the importance of testing for DPD deficiency before initiation of the treatment.

Fluoropyrimidines are a group of anti-cancer medicines including 5-fluorouracil and its prodrugs capecitabine and tegafur.

A recent European safety review has recommended that despite uncertainties in the optimal pre-treatment testing methodologies, all patients should undergo testing for DPD deficiency prior to the initiation of these treatments.

Fluorouracil is also available in topical formulations, but due to very low systemic absorption via this route, DPD testing is not required prior to initiation.

Up to 17 June 2020, 30 reports associated with a fatal outcome that describe a known or suspected DPD deficiency with fluorouracil and capecitabine have been received. These include reports of testing and confirmation of DPD deficiency after patients were treated with capecitabine and developed severe and fatal toxicity.

Health-care professionals should test all patients for DPD deficiency before initiation of treatment. Patients with known complete DPD deficiency should not be treated with these medicines. For patients with partial DPD deficiency, a reduced starting dose should be considered.

All patients should be monitored for toxicity particularly during the first cycle of treatment or after a dose increase.

***Reference:***
Drug Safety Update, MHRA, 22 October 2020 *(www.gov.uk/mhra)*

*(See also WHO Pharmaceuticals Newsletter No.2, 2020: Pre-treatment testing recommended for cancer in Europe)*

## Glatiramer

### Risk of hepatic impairment

**Japan.** The MHLW and the PMDA have announced that the package inserts for glatiramer (Copaxone S.C.®) should be revised to include hepatic impairment as an adverse drug reaction.

Glatiramer is indicated to prevent relapse of multiple sclerosis.

One case of hepatic impairment in a patient treated with glatiramer has been reported in Japan during the previous three years, for which a causal relationship between the drug and event was reasonably possible. No patient mortalities have been reported.

Liver function tests should be performed prior to the initiation and periodically during the administration of glatiramer.

***Reference:***
Revision of Precautions, MHLW/PMDA, 5 November 2020 *(www.pmda.go.jp/english/)*

## Insulin

### Risk of cutaneous amyloidosis at injection site

**United Kingdom.** The MHRA has announced that the SmPC and PIL for all insulin-containing products are being updated to include the risk of cutaneous amyloidosis at injection site.

Insulin is indicated to treat all types of diabetes including type I and II diabetes and gestational diabetes.

In the UK, up until the end of July 2019, two reports of cutaneous amyloidosis in patients receiving insulin therapy have been received.

Patients who inject insulin at the same site regularly, are at an increased risk of developing cutaneous amyloidosis at the injection site and consequently may have poor diabetes control as the amyloid causes absorption to decrease. Health-care professionals should advise patients to rotate injection sites within the same body region to prevent the risk.

There also is a risk of hypoglycaemia in patients that suddenly change injection site from an area with cutaneous amyloidosis to an unaffected area. Health-care professionals should advise patients to carefully monitor blood glucose after a change in injection site and that dose adjustment of

insulin or other antidiabetic medication may be needed.

***Reference:***
Drug Safety Update, MHRA, 23 September 2020 (www.gov.uk/mhra)

## Methotrexate

### New measures to reduce risk of fatal overdose

**United Kingdom.** The MHRA has announced that new measures have been implemented to reduce the risk of fatal overdose of methotrexate.

Methotrexate is indicated to treat autoimmune conditions and should be taken once a week.

Since January 2006 up to July 2020, the MHRA received 11 cases of serious toxicity associated with inadvertent daily dosing of once-weekly methotrexate in the UK, with four of these serious reports received since January 2016.

Overdose of methotrexate can lead to serious adverse drug reactions such as haematopoietic disorders and gastrointestinal reactions.

The product information and outer and inner packaging of methotrexate for once-weekly dosing will carry a warning about the dosing schedule and the consequences of dosing errors.

Also, methotrexate products will come with a patient card, which will prompt patients to take methotrexate once a week and to record the day of the week for intake.

Educational materials for health-care professionals will also be made available for oral products with indications requiring once-weekly dosing.

***Reference:***
Drug Safety Update, MHRA, 23 September 2020 (www.gov.uk/mhra)

*(See also WHO Pharmaceuticals Newsletter No.1, 2020: New measures to avoid dosing errors in Ireland)*

## Niraparib

### Risk of severe hypertension and posterior reversible encephalopathy syndrome (PRES)

**United Kingdom.** The MHRA has announced that the product information for niraparib (Zejula®) has been updated to strengthen the warning of the risk of severe hypertension and posterior reversible encephalopathy syndrome (PRES).

Niraparib is indicated as monotherapy for the maintenance treatment of adults with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.

A recent European review identified worldwide reports of patients who developed severe hypertension including rare cases of hypertensive crisis. Also the review identified rare reports of PRES.

The product information for niraparib had an existing warning for hypertension including hypertensive crisis and recommended that blood pressure should be monitored monthly in the first year. Based on the review safety warnings have been updated to recommend more frequent blood pressure measurements, especially at the start of treatment.

In the UK, up to 30 July 2020, six reports of hypertension associated with niraparib were received. No reports have been received for PRES associated with niraparib.

Health-care professional should control pre-existing hypertension adequately before treatment and monitor blood pressure from initiation. Also, the use of niraparib should be discontinued in case of hypertensive crisis of PRES.

***Reference:***
Drug Safety Update, MHRA, 22 October 2020 (www.gov.uk/mhra)

## Nivolumab (genetic recombination)

### Risk of fulminant hepatitis

**Japan.** The MHLW and the PMDA have announced that the package insert for nivolumab (genetic recombination) (Opdivo®) should be revised to include fulminant hepatitis as an adverse drug reaction.

Nivolumab is indicated to treat a number of cancers including malignant melanoma, unresectable or metastatic renal cell carcinoma, relapsed or refractory classical Hodgkin lymphoma and relapsed or metastatic head and neck cancer.

A total of 18 cases involving fulminant hepatitis in patients treated with nivolumab have been reported in Japan during the previous three years, of which a causal relationship between the drug and event was reasonably possible in three cases. A total of 10 patient mortalities have been reported to date, which a causal relationship between the drug and event was reasonably possible in three cases.

Fulminant hepatitis, hepatic failure, hepatic impairment, hepatitis and sclerosing cholangitis may occur. Patients should be carefully monitored through periodic liver function tests.

***Reference:***
Revision of Precautions, MHLW/PMDA, 5 November 2020 (www.pmda.go.jp/english/)

## Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

### Risk of kidney problems with foetal exposure

**USA**. The US FDA has announced that it is requiring changes to the prescribing information for nonsteroidal anti-inflammatory drugs (NSAIDs) and will update the Drug Facts labels to warn about rare but serious kidney problems in unborn babies with the use of NSAIDs around 20 weeks or later in pregnancy.

NSAIDs are some of the most commonly used medicines for pain and fever and used to treat medical conditions such as arthritis, menstrual cramps, headaches, colds and the flu. Examples of NSAIDs include aspirin, ibuprofen, naproxen, diclofenac and celecoxib. Also, common adverse effects of NSAIDs include stomach pain, constipation, diarrhoea, gas, heartburn, nausea, vomiting and dizziness.

Health-care professionals should limit prescribing NSAIDs between 20 to 30 weeks of pregnancy and avoid prescribing them after 30 weeks of pregnancy. Ultrasound monitoring of amniotic fluid should be considered if NSAID treatment extends beyond 38 hours and NSAIDs should be discontinued if oligohydramnios is found.

Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. If NSAID treatment is deemed necessary between 20 to 30 weeks of pregnancy, it use should be limited to the lowest effective dose and shortest duration possible.

***Reference:***
MedWatch, US FDA, 15 October 2020 *(*www.fda.gov*)*

*(See also WHO Pharmaceuticals Newsletter No.1, 2015: Risks during pregnancy in US)*

## Opioids

### Risk of dependence and addiction

**United Kingdom.** The MHRA has announced that the CHM has made recommendations on including warnings on packages of opioids about the risk of dependence and addiction.

Opioids are used in the treatment of pain. More than 20 different opioid medicines are authorised in the UK, including alfentanil, dihydrocodeine, meptazinol, oxycodone, fentanyl and morphine.

The CHM convened an expert working group to examine the benefits and risks of opioids in the relief of no-cancer pain. The CHM recommended that the packaging for all opioid medicines in the UK carries the warnings "can cause addiction" and "contains opioid".

Health-care professionals should inform patients of the potential of drug dependence and addiction with the prolonged use of opioids, even at therapeutic doses. Typical signs of addiction include expression of cravings for the drug and experiencing withdrawal adverse effects when opioids are stopped suddenly.

Withdrawal from an opioid is characterised by shivers, diarrhoea, insomnia and myalgia. To minimize the risk of withdrawal reactions, the dose of opioid should be tapered slowly at the end of treatment.

Also, opioids readily cross the placenta, and therefore if used during pregnancy neonates may become dependent and experience neonatal abstinence syndrome at birth. Extra vigilance is required.

***Reference:***
Drug Safety Update, MHRA, 23 September 2020 *(*www.gov.uk/mhra*)*

*(See also WHO Pharmaceuticals Newsletter No.3, 2019: Risk of uncontrolled pain and withdrawal symptoms following sudden discontinuation in US)*

## Ticagrelor

### Potential risk of central sleep apnea

**Canada**. Health Canada has announced that it has requested the manufacturer of ticagrelor (Brilinta®) to update the safety information to add a warning about the potential risk of central sleep apnea (CSA).

Ticagrelor is used with low-dose acetylsalicylic acid (e.g. aspirin) to decrease the risk of having a stroke or dying from heart or blood vessel disease.

Triggered by the publication of two confirmed cases of CSA, Health Canada reviewed the available information from searches of the Canada vigilance database, international databases and published literature. Also, Health Canada has reviewed two Canadian reports of CSA related to ticagrelor use, but these reports did not have enough information to be assessed.

Health Canada's review of the available information concluded that there may be a link between the use of ticagrelor and the risk of CSA.

***Reference:***
Summary Safety Review, Health Canada, 28 October 2020 *(*www.hc-sc.gc.ca*)*

## Tofacitinib

### Risk of venous thromboembolism and infections

**Ireland.** The HPRA has announced that the product information (SmPC and PL) for tofacitinib (Xeljanz®) has been updated to reflect the risk of

venous thromboembolism (VTE), serious and fatal infections.

In May 2019, the EMA's PRAC recommended that 10 mg twice daily dose of tofacitinib should be contraindicated in patients at high risk of pulmonary embolism (PE) as a temporary measure following the conclusions of a review of the risk of VTE and all-cause mortality in patients treated with tofacitinib and

Tofacitinib is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis (UC).

The PRAC review was concluded and temporary measures have been updated to minimize the risks of VTE and serious infections associated with use of tofacitinib. A dose-dependent increased risk of serious VTE has been observed in patients taking tofacitinib.

For treatment of rheumatoid arthritis and psoriatic arthritis, the recommended dose of 5mg twice daily should be not exceeded.

Patients should be informed of the signs and symptoms of VTE before they start tofacitinib therapy and advised to seek prompt medical help if they develop these symptoms during treatment. Also, patients over 65 years are at increased risk of serious infections and mortality due to infections.

***Reference:***
Drug Safety Newsletter, HPRA, September 2020 (www.hpra.ie)

*(See also WHO Pharmaceuticals Newsletter No.4, 2020: Risk of blood clots in the deep veins in Canada; No.3, 2020: Risk of venous thromboembolism and serious and fatal infections in UK; No.6, 2019: Risk of blood clots in EU; No.5, 2019)*

## Torsemide (oral)

### Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome

**Republic of Korea**. The MFDS has updated the drug label for oral torsemide products to include the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Torsemide is a potent loop diuretic commonly used in patients with congestive heart failure.

During the evaluation process of SAE reports, the KIDS reviewed one fatal SAE report from adverse drug reaction relief system which suggested a link between torsemide and DRESS syndrome. The signal detected from the SAE report was re-assessed through a routine signal analysis process.

At the time of review, the KIDS had received five domestic reports of DRESS syndrome with torsemide use through the Korean adverse event reporting system since 1989. Data mining results of the reports within the database identified a statistical association between torsemide and DRESS syndrome. Subsequent case evaluation was performed on these reports, in which causal association could not be excluded.

This recommendation announced by the MFDS was based on the results of SAE review system, signal analysis and evaluation procedure at the KIDS.

***Reference:***
Based on the communication from MFDS and KIDS, Republic of Korea, November 2020

## Ulipristal acetate

### Risk of liver injury: restricting use recommended

**Europe**. The EMA has announced that due to serious liver injury the use of ulipristal (Esmya® and generic) should be restricted to treat uterine fibroids in premenopausal women for whom surgical procedures are not appropriate or have not worked. Ulipristal must not be used for controlling symptoms of uterine fibroids while awaiting surgical treatment.

Ulipristal is indicated to treat moderate to severe symptoms of uterine fibroids in women who had not reached the menopause.

EMA's PRAC reviewed the risk of liver injury and found that it was not possible to identify either patients at risk of liver injury or measures that could reduce the risk. The PRAC had therefore advised that ulipristal should not be marketed in the EU.

The Committee for Medicinal Products for Human Use (CHMP) endorsed the PRAC's assessment of the risk of liver injury, but considered that the benefits of ulipristal in controlling fibroids may outweigh the risk in women who have no other treatment options and recommended the restricting use of ulipristal.

Ulipristal is also used for emergency contraception. No concern has been raised about liver injury for this use.

Information on the risk of liver failure will be added to the SmPC and PL for ulipristal.

***Reference:***
EMA, 13 November 2020 (www.ema.europa.eu)

*(See also WHO Pharmaceuticals Newsletter No.5, 2020: Revocation of marketing authorizations recommended in Europe; No.3, 2020: Licence suspension due to liver injury in UK; No.1, 2020: Risk of hepatic injury in EU)*

## Vascular endothelial growth factor (VEGF) pathway inhibitors

### Risk of aneurysm and artery dissection

**Ireland.** The HPRA has announced that the product information (SmPC and PL) for all vascular endothelial growth factor (VEGF) pathway inhibitors have been updated to reflect the risk of aneurysm and artery dissection.

VEGF pathway inhibitors are indicated to block tumour angiogenesis and tumour growth. VEGF pathway inhibitors include aflibercept (Zaltrap®), axitinib (Inlyta®), bevacizumab (Avastin®), lenvatinib (Kisplyx®) and ponatinib (Iclusig®).

The EMA's PRAC has completed a review of VEGF pathway inhibitors with respect to the potential risk of aneurysm and artery dissection. Prior to the review, the product information for a number of VEGF pathway inhibitors already included warnings regarding the risk of aneurysm and artery dissection.

Based on the review, the product information for all VEGF pathway inhibitors for systemic administration have been updated to reflect the risk. However, the review concluded a causal association could not be established between these risks and the two VEGF pathway inhibitors, ranibizumab (Lucentis®) and aflibercept (Eylea®).

Health-care professionals are advised that the use of VEGF pathway inhibitors for systemic administration in patients with or without hypertension may promote the formation of aneurysm and artery dissection, which may be fatal in some cases.

***Reference:***
Drug Safety Newsletter, HPRA, September 2020 *(www.hpra.ie)*

*(See also WHO Pharmaceuticals Newsletter No.1, 2019: Risk of artery dissections and artery aneurysms in Canada; No.1, 2015: Thrombotic microangiopathy in Canada)*

## Vonoprazan

### Risk of shock, anaphylaxis and hepatic impairment

**Japan.** The MHLW and the PMDA have announced that the package inserts for vonoprazan containing products (Takecab®, Vonosap® and Vonopion®) should be revised to include shock, anaphylaxis and hepatic impairment as adverse drug reactions.

Vonoprazan is indicated: to treat and prevent gastric and duodenal ulcers, to treat reflux esophagitis and to be included as part of a *Helicobacter pylori* eradication regimen.

A total of 18 cases of shock or anaphylaxis in patients treated with vonoprazan have been reported in Japan during the previous three years, one of which a causal relationship between the drug and event was reasonably possible. No patient mortalities have been reported to date.

Also, a total of 41 cases of hepatic impartment reported in patients exposed to vonoprazan have been reported, of which a causal relationship was reasonably possible in seven cases. Four patient mortalities have been reported, a causal relationship with the drug and event could not be established in any of the four cases.

Patients should be carefully monitored, and if any abnormalities are observed the drug should be discontinued and appropriate measures should be taken.

The MHLW and PMDA have concluded that a revision of the package insert was necessary.

***Reference:***
Revision of Precautions, MHLW/PMDA, 6 October 2020 *(www.pmda.go.jp/english/)*

## Bupropion

### Possible risk of psoriasis exacerbation

**New Zealand.** Medsafe is highlighting a possible risk of psoriasis exacerbation with the use of bupropion (Zyban®) to encourage further reporting so that more information on this potential safety concern can be obtained.

Bupropion is indicated to aid smoking cessation. It works by inhibiting the reuptake of noradrenaline and dopamine in the nervous system.

This potential safety concern was triggered by a report received by the Center for Adverse Reactions Monitoring (CARM). The reports describe the exacerbation of psoriasis 15 days after starting bupropion.

Psoriasis is a chronic inflammatory skin condition, and drug induced psoriasis occurs more frequently in patients with a history of smoking, obesity, diabetes, hypertension and dyslipidaemia.

There are some published case reports of people with pre-existing and well-controlled psoriasis who have had an exacerbation of their psoriasis within two weeks of starting bupropion. In most cases, the exacerbation resolved when bupropion was stopped.

***Reference:***
Safety Communication, Medsafe, 29 September 2020 (*www.medsafe.govt.nz/*)

## Diphenhydramine

### Risk with high doses

**USA**. The US FDA has announced that taking higher than recommended doses of diphenhydramine (Benadryl®) can lead to serious heart problems, seizures, coma or even death.

Diphenhydramine is an antihistamine used to temporarily relieve symptoms due to hay fever, upper respiratory allergies, runny nose and sneezing.

The FDA is aware of news reports of teenagers ending up in emergency rooms or dying after participating in the "Benadryl Challenge" encouraged in videos posted on the social media.

Health-care professionals should be aware that the "Benadryl Challenge" is occurring among teens and alert their caregivers about it. In the event of an overdose, health-care professionals should attempt to determine whether a patient with a suspected overdose took diphenhydramine.

***Reference:***
MedWatch, US FDA, 24 September 2020 (*www.fda.gov*)

*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 24 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. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 16). 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, on the UMC Measures of Disproportionate Reporting etc., visit 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.*

# Dronedarone-induced hyperkalemia

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**Summary**

Hyperkalemia associated with dronedarone was identified as a potential signal in a screening of VigiBase, the WHO global database of individual case safety reports, at the Uppsala Monitoring Centre (UMC). As of April 2019, there were 18 unique cases from ten countries reporting hyperkalemia with dronedarone as a suspected or interacting medicine (expected eight). Dronedarone was the only product suspected in 12 cases. The average time from dronedarone start to the event onset (TTO) was 19 days (n=11), ranging from three days to nine weeks. Positive dechallenge was reported in six cases. In 11 cases, (acute) renal failure was a co-reported event, with creatinine increased in two other cases, while in five cases there were no co-reported renal events and in four of these only dronedarone was suspected. Other drugs known to cause hyperkalemia were reported as suspected (four cases) or concomitant drugs (ten cases), such as beta-blockers and calcium channel blockers (which alter transmembrane potassium movement); ACE-inhibitors, angiotensin-II receptor blockers, NSAIDs, and potassium-sparing diuretics (which impair renal potassium excretion); and potassium-containing agents (which increase supply of potassium).

Based on the Bradford-Hill criteria, and especially the reporting disproportionality (observed 18 and expected eight), a close temporal relationship including positive dechallenge, and similar literature cases, a causal relationship for dronedarone and hyperkalemia seems possible. The mechanism is unclear, but likely to be multifactorial: e.g. renal failure with dronedarone and concomitant medications known to cause hyperkalemia as contributing factors. Health care professionals should be aware of this possible risk. Renal function should be monitored periodically as recommended during dronedarone treatment.

**Introduction**

Dronedarone is an anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds including amiodarone. Dronedarone (Multaq) is approved for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF) in the European Union (EU). Due to its safety profile (as highlighted in the sections of contraindication and warnings in the product information), dronedarone should only be prescribed after alternative treatment options have been considered. The recommended dose is 400 mg twice daily in adults.[1]

Hyperkalemia is a common clinical condition that can be defined as a serum potassium concentration exceeding 5.0 mmol/L. Hyperkalemia becomes a potentially life-threatening condition where serum potassium exceeds 5.5 mmol/l. It can be caused by reduced renal excretion, or excessive intake or

leakage of potassium from the intracellular space. In addition to acute and chronic renal failure, hypoaldosteronism, and massive tissue breakdown (as in rhabdomyolysis), are typical conditions leading to hyperkalemia. Symptoms are non-specific and predominantly related to muscular or cardiac dysfunction.[2-4]

Drug-induced hyperkalemia is the most important cause of increased potassium levels in everyday clinical practice; it may be asymptomatic. However, it can be dramatic and life threatening, posing diagnostic and management problems. A wide range of drugs can cause hyperkalemia by a variety of mechanisms. Drugs can interfere with potassium homoeostasis either by altering transmembrane potassium movement or by impairing renal potassium excretion. Drugs may also increase potassium supply. The reduction in renal potassium excretion due to inhibition of the renin-angiotensin-aldosterone system represents the most important mechanism by which drugs are known to cause hyperkalemia[5].

- Medications that alter transmembrane potassium movement include amino acids, beta-blockers, calcium channel blockers, suxamethonium, and mannitol.
- Drugs that impair renal potassium excretion are mainly represented by ACE-inhibitors, angiotensin-II receptor blockers, direct renin inhibitors, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors (NSAIDs), heparin and derivatives, aldosterone antagonists, potassium-sparing diuretics, trimethoprim, and pentamidine.
- Potassium-containing agents represent another group of medications causing hyperkalemia.

The combination of dronedarone and hyperkalemia was detected in a screening of VigiBase, the WHO global database of individual case safety reports, at the Uppsala Monitoring Centre (UMC). The Bradford-Hill criteria were applied in the assessment of the case series to evaluate causality and possible risk factors for dronedarone associated hyperkalemia.

**Reports in VigiBase**

A clinical review of reports with hyperkalemia associated with dronedarone included in VigiBase up to April 2019 was performed; duplicates were excluded.

VigiBase contained 18 unique cases reporting hyperkalemia with dronedarone as a suspected or interacting medicine (expected eight). Dronedarone was the only suspected drug in 12 cases. The reports came from 10 countries (six from the USA, three from Sweden, two from the Republic of Korea, and one each from Austria, Germany, Italy, the Netherlands, Slovakia, Slovenia, and the United Kingdom). There were five females and 13 males, with an age range between 45 and 86 years (mean 71). The dronedarone dose was known in 11 cases: 400 mg once daily in two cases and twice daily in nine cases. A total of 89% (n=16) of the cases were serious, with four life-threatening and one fatal. When the information on potassium value was available, the maximum levels were reported as 5.4, 5.7, 6.0, 6.2, 7.1 and >7 mmol/L, respectively.

Where given (n=11), the average TTO was 19 days (SD=18) ranging from three to 63 days (not included TTO=6 years in a case reported by a non-physician with limited information, and TTO as "weeks" in one case). Positive dechallenge was reported in six cases when information was available. Based on the temporal relationship including positive dechallenge, there seems to be a possible causal relation for dronedarone associated hyperkalemia.

In 11 cases, (acute) renal failure was a co-reported event, with creatinine increased in two other cases, while in five there were no co-reported renal events and in four of these only dronedarone was suspected. While creatinine increased is clearly included in the label as an adverse reaction of dronedarone, renal failure is not.

Other drugs known to cause hyperkalemia were reported as suspected (four cases) or concomitant (10 cases): such as beta-blockers and calcium channel blockers (alter transmembrane potassium movement); ACE-inhibitors, angiotensin-II receptor blockers, NSAIDs, potassium-sparing diuretics (impair renal potassium excretion); and potassium-containing agents (increase potassium supply).

**Literature and labelling**

Hyperkalemia is not labeled in the product information.[1] Section 4.8 Undesirable effects mentions "Plasma creatinine increase ≥10% five days after treatment initiation" as very common.

In section 4.4 Special warnings and precautions for use the following is described: "Larger increases in creatinine after dronedarone initiation have been reported in the post-marketing setting. Some cases also reported increases in blood urea nitrogen possibly due to hypoperfusion secondary to developing CHF (pre-renal azotaemia). In such cases dronedarone should be stopped (see sections 4.3 and 4.4). It is recommended to monitor renal function periodically and to consider further investigations as needed."

**Discussion**

Dronedarone is a non-iodinated benzofuran developed specifically for the treatment of AF, designed to retain the efficacy of amiodarone, but with an improved safety profile.[6] However, due to its safety profile, dronedarone should only be prescribed after alternative treatment options have been considered.[1]

Based on 18 unique cases in VigiBase reported from 10 different countries, the close temporal relationship including cases with positive dechallenge seems to support a possible causal association between dronedarone use and hyperkalemia.

The etiology of hyperkalemia is often multifactorial, with impaired renal function, medication use, and hyperglycemia as the most common contributory factors.[7, 8]

The mechanism behind the possible causal relationship between dronedarone use and hyperkalemia is not clear. In 11 of the 18 cases, (acute) renal failure was a co-reported adverse event, with creatinine increased in two other cases. Therefore, renal impairment might have contributed to the occurrence of hyperkalemia following dronedarone treatment. Currently, renal failure is not specifically labeled in the EU Summary of Product Characteristics of dronedarone[1] (Multaq). However, "Blood creatinine increased" is a well-known adverse reaction with a frequency as "very common": "≥ 10% five days after treatment initiation". There are also detailed warnings on "Management of plasma creatinine increase". As post-marketing experiences, "increases in blood urea nitrogen possibly due to hypoperfusion secondary to developing congestive heart failure (pre-renal azotaemia)" is also mentioned.

Potassium is the most abundant intracellular cation (100 - 150 mmol/l) and is critical in many physiological functions. In healthy subjects[9], dronedarone reduces renal creatinine and N-methylnicotinamide (NMN) clearance by about 18%, without evidence of an effect on glomerular filtration rate, renal plasma flow or electrolyte exchanges. This suggests a specific partial inhibition of tubular organic cation transporters. A limited increase in serum creatinine is therefore expected with dronedarone treatment but does not mean there is a decline in renal function. It was stated that no clinically relevant changes were observed in the laboratory tests. No changes in urine flow rate, osmolality, sodium and potassium excretions were observed between the baseline and day 7 of dronedarone treatment compared with placebo. However, no results have been presented on potassium levels.

Dronedarone and renal impairment has been evaluated in the Italian[10] as well as Spanish post-marketing reports, together with review of the literature.[11] Tarapués et al[11] showed that the reporting odds ratio was 2.88 (1.52-5.46). Positive dechallenge was observed in five of ten cases. In addition, eight cases of renal failure were found in the medical literature. It was concluded that the effect of dronedarone on the renal function is supported by limited information; and based on cases from spontaneous reporting systems and those from the medical literature, there was a potential relationship between dronedarone use and renal impairment.

In 2012, Biagi et al[10] reported nine cases of renal impairment (mostly acute renal failure) among the Italian post-marketing reports of dronedarone. Interestingly, three cases of hyperkalemia were noted (blood potassium levels 5 mmol/l, 5.6, and 9.6 mEq/l, respectively). However, none of these 18 hyperkalemia cases in VigiBase were reported from Italy, indicating an under-estimation of the dronedarone-related hyperkalemia, either due to under-reporting, or due to incomplete coding of cases or searches in VigiBase.

In addition to renal impairment as a contributing factor, other medication use, and hyperglycemia may also play a role as risk factors. There were concomitant medications known to cause hyperkalemia such as beta-blockers and calcium channel blockers, ACE-inhibitors, angiotensin-II receptor blockers and potassium-sparing diuretics. Among the 18 cases, seven were taking medications for diabetes, although hyperglycemia was not specifically mentioned.

**Conclusion**

Based on the Bradford-Hill criteria, and especially the reporting disproportionality, close temporal relationship including positive dechallenge, and similar literature cases, a causal relationship for dronedarone and hyperkalemia seems possible. The mechanism is unclear, but likely to be multifactorial, e.g. renal failure with dronedarone and concomitant medications known to cause hyperkalemia as contributing factors. Health care professionals should be aware of this possible risk. Renal function should be monitored periodically as recommended during dronedarone treatment.

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# CAVEAT DOCUMENT

***Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs).***
*Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.*

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 Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

**Tentative and variable nature of the data**

*Uncertainty*: 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 is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

*Variability of source*: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

*Contingent influences*: 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 adverse effects and other factors.

*No prevalence data*: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

*Time to VigiBase*: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

**For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.**

**Prohibited 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 VigiBase must include a statement:**

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or 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.

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# COVID-19 vaccines: Safety Surveillance Manual

The 42nd Global Advisory Committee on Vaccine Safety (GACVS) virtual meeting on 27–28 May 2020 addressed pharmacovigilance preparedness for the launch of future COVID-19 vaccines. One of the recommendations made was: that infrastructure and capacity for surveillance of the safety of COVID-19 vaccines should be in place in all countries and existing infrastructure be reactivated and engaged before a vaccine is introduced. This will require local, national, regional and global collaboration. Countries should include preparedness plans for COVID-19 vaccine safety in their overall plans for vaccine introduction, building on WHO guidance.

Following recommendations and guidance of the GACVS members, as well as experts from around the world, the "COVID-19 vaccines: Safety Surveillance Manual" has been developed and will be soon made publicly available[1].

The manual aims to provide guidance to ensure Member States have 1) preparedness plans for monitoring the safety of COVID-19 vaccines before they are deployed and 2) communication strategies about COVID-19 vaccine safety. The target audience include: governments, global, regional and national staff from immunization programmes, regulatory authorities, ministries of health, partners and Pharmacovigilance centres as well as vaccine manufactures.

The objectives of the manual are to:

- provide an overview of COVID-19 vaccines likely to be available and their characteristics;
- identify the safety implications for the potential priority populations and immunization strategies;
- identify all stakeholders, including vaccine marketing authorisation holders;
- provide guidance on how the stakeholders can collaborate to ensure transparent collection, analyses and sharing of COVID-19 vaccine safety data;
- define the elements of COVID-19 vaccine pharmacovigilance preparedness and to identify current capacities and gaps in countries;
- provide guidance for enhancing and harmonizing vaccine safety surveillance systems, to guide processes for collecting, analysing and sharing safety data and information, including data management systems;
- support evidence-based programmatic decisions related to COVID-19 vaccines; and
- provide guidance to support vaccine safety communication during COVID-19 pandemic.

The manual incorporates current and available information that is critical for all stakeholders before, during and after the introduction of COVID-19 vaccines and is comprised of nine modules which can be consulted individually or as a single document:

- COVID-19 vaccines: description and general safety considerations for implementation
- Stakeholders in COVID-19 vaccine safety surveillance
- Establishing surveillance systems in countries using COVID-19 vaccines
- Monitoring and responding to adverse events following immunization (AEFIs)
- Monitoring and responding to adverse events of special interest (AESIs)
- Safety data management systems in countries using COVID-19 vaccines
- Engaging with the pharmaceutical industry for COVID-19 vaccine safety surveillance
- Regulatory reliance and work-sharing
- COVID-19 vaccine safety communication

Given the rapidly evolving landscape, information will be updated as frequently as needed. For this reason, only an online electronic version will be made available.

[1] Now available at: https://www.who.int/publications/i/item/10665338400

# The Vaccine Safety Net (VSN) Virtual Meeting

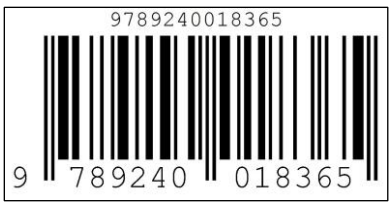
The Vaccine Safety Net (VSN) is a global network of websites aiming to facilitate the access to reliable, evidence-based information on the safety of vaccines for online users, regardless of their geographic location and language. The VSN is unique in terms of its geographic outreach and its ability to reach a wide audience globally. The diversity of institutions composing the network, as well as their expertise in cultural and public health contexts place it as a key player in the vaccine safety communication landscape.

In August 2020, the VSN secretariat conducted a survey to identify the needs of the VSN members to support their communication efforts on the safety of COVID-19 vaccines. The survey identified a gap on COVID-19 vaccines' safety resources more particularly on vaccines' platforms, ingredients, administration, targeted population, effectiveness, roll out, as well as expected adverse events and safety information regarding routine vaccination in the COVID-19 context. VSN members expressed also the need to share knowledge and expertise on communication strategies including innovative approaches to facilitate the dissemination of reliable and understandable information on COVID-19 vaccines' safety.

In May 2020, during the 42nd Global Advisory Committee on Vaccine Safety (GACVS) virtual meeting, GACVS made a recommendation: that infrastructure and capacity for surveillance of the safety of COVID-19 vaccines should be in place in all countries and existing infrastructure be reactivated and engaged before a vaccine is introduced. A COVID-19 vaccines safety guidance manual including guidance on communication activities has been developed and is now under finalization upon recommendation and guidance of GACVS members and key experts.

This is in this context that the VSN virtual meeting will take place on 8$^{th}$ and 10$^{th}$ December 2020 with the objectives of defining how VSN members could play a critical role in the dissemination of COVID-19 vaccine safety information. The meeting aims to (1) take stock of the progress made and the data obtained so far to start coordinating active communications/messaging on COVID-19 vaccine safety and to identify additional elements that should be further developed to improve vaccine safety related messaging and content; (2) learn from innovative approaches and communication strategies already used by VSN members to address COVID-19 vaccines safety related questions and to identify key lessons learned and; (3) define concrete action points for the VSN members and the VSN secretariat to tackle specific situations.

Based on the outcome of this meeting, a detailed communication plan will be developed for the Vaccine Safety Net and key activities will be identified to further strengthen the role of VSN in COVID-19 vaccines safety communication in close collaboration with other WHO departments involved in communication activities. This meeting will also help to identify additional resources and tools to be shared by the VSN secretariat with VSN members to support this communication effort. Lessons learned from innovative approaches and communication strategies already used by some countries/members will help inform further VSN activities in relation to COVID-19 vaccines safety and routine immunization. This will also help VSN members and the VSN secretariat to translate the vaccine safety surveillance manual proposed scenarios into concrete actions.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