## Safety news

### Restrictions

**Mirabegron: contraindicated in patients with severe hypertension**

**United Kingdom** – The marketing authorization holder, in consultation with the MHRA, has informed health professionals of cases of severe hypertension reported in patients taking mirabegron (Betmiga®), including hypertensive crisis associated with cerebrovascular and cardiac events (mainly transient ischaemia attack or stroke). Mirabegron is now contraindicated in patients with severe uncontrolled hypertension with a systolic blood pressure of 180 mm Hg or higher and/or a diastolic blood pressure of 110 mm Hg or higher. Blood pressure should be measured before starting treatment and periodically during treatment, especially in patients with hypertension.

Mirabegron is used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome. It is known that mirabegron can increase blood pressure. Health professionals were also reminded of restrictions in the use of mirabegron in patients with renal impairment and in those with hepatic impairment who are also taking strong inhibitors of cytochrome P450 3A such as itraconazole, ketoconazole, ritonavir, or clarithromycin, as this will lead to increased exposure (area under the curve, AUC) of mirabegron.


### Safety warnings

**Proton pump inhibitors: subacute cutaneous lupus erythematosus**

**United Kingdom** – The MHRA has warned that proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE), especially in sun-exposed areas of the skin.

Health professionals should suspect SCLE in patients treated with a proton pump inhibitor who develop such lesions and who report arthralgia. Treatment discontinuation should be considered unless it is imperative for a serious acid-related condition. In most cases, symptoms resolve on PPI withdrawal. If there are no signs of remission after a few weeks or months, treatment with topical or systemic steroids may be necessary.


**Antiviral combinations for hepatitis C: liver injury**

**United States of America** – The FDA has warned about the risk of potentially serious liver injury in patients taking one of two antiviral fixed-dose combination products used to treat chronic hepatitis C: dasabuvir, ombitasvir, paritaprevir, and ritonavir (Viekira Pak®) and ombitasvir, paritaprevir, and ritonavir (Technivie®). Information about this safety risk has been added to the product information for the two medicines.

Technivie® is FDA-approved for use in patients with genotype 4 chronic hepatitis C.
C virus infection without cirrhosis, while Viekira Pak® is FDA-approved for use in patients with genotype 1 chronic hepatitis C infection including those with compensated cirrhosis. Serious outcomes were reported mostly in patients taking Viekira Pak® who had evidence of advanced cirrhosis before starting treatment with the drug. (1)

Canada – In response to new international safety information about serious cases of liver injury, Health Canada has recommended updates to product information for the fixed-dose combination of ombitasvir/paritaprevir/ritonavir and dasabuvir (Holkira Pak®) and the fixed-dose combination of ombitasvir/paritaprevir/ritonavir (Technivie®). (2)

► (1) FDA Drug safety communication. 22 October 2015.
► (2) Health Canada Advisory, 10 November 2015.

Daclatasvir hydrochloride and asunaprevir: interstitial pneumonia
Japan – The PMDA has requested that product information for daclatasvir hydrochloride (Daklinza®) and asunaprevir (Sunvepra®) should be updated to include information about the risk of interstitial pneumonia in patients treated with a combination of the two medicines. This follows 11 cases reported in Japan in the last three years, including four where causality could not be ruled out.

► PMDA Summary of investigation results and Revision of Precautions, 20 October 2015.

Vemurafenib: potentiation of radiation toxicity
United Kingdom – The MHRA has alerted prescribers to the risk of potentiation of radiation toxicity in patients treated with radiation before, during, or following treatment with vemurafenib (Zelboraf®). Vemurafenib should be used with caution in such patients.

The risk was identified in a review of worldwide data by EU medicines regulators. Severe cases of radiation-related injuries, including some with fatal outcome, have been reported. In the majority of cases, patients received radiotherapy regimens greater than or equal to 2 Gy/day. The events included radiation recall and radiation sensitization. Most cases were cutaneous in nature but some cases involved visceral organs.


Crizotinib: heart failure
United Kingdom – The MHRA has warned health professionals about the risk of severe and potentially fatal cardiac failure in patients treated with crizotinib (Xalkori®) identified in a review by European medicines regulators.

Health professionals should monitor all patients for signs and symptoms of heart failure, including dyspnoea, oedema, or rapid weight gain from fluid retention. A dose reduction, treatment interruption or treatment discontinuation should be considered if any of these symptoms occur.

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► PMDA Summary of investigation results and Revision of Precautions, 20 October 2015.
Fingolimod: skin cancer
Canada – Health Canada has approved updates to the product information for the multiple sclerosis drug fingolimod (Gilenya®) to warn about two specific risks associated with the medicine’s action on the immune system.

A Health Canada safety review found that fingolimod may increase the risk of cancers, particularly of the skin. Patients and health professionals should be vigilant for symptoms of skin cancer.

Information on the risk of progressive multifocal leukoencephalopathy (PML), as reported in the EU and the U.S. earlier this year, was also added. The risk of lymphoma and of infections was already mentioned in the Canadian monograph.

► Health Canada Advisory, 30 September 2015.

Aripiprazole: impulse control disorders
Canada – Health Canada has approved updates to the product information of aripiprazole (Abilify®) to include a warning about an increased risk of impulsive behaviours of pathological gambling and hypersexuality. (1)

Aripiprazole tablets are authorized to treat a serious type of bipolar disorder, schizophrenia and related severe psychotic disorders and major depressive disorder in adults when used in combination with other drugs. The solution for injection is used for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate. A long-acting product (Aristada®, Abilify Maintena®) – a prolonged-release suspension for injection – is used for maintenance treatment of schizophrenia in adults.

► (1) Health Canada Advisory, 2 November 2015.

Sodium polystyrene sulfonate: separate dosing to prevent interactions
United States of America – The FDA has informed health professionals that additional studies are being required for the potassium-lowering medicine sodium polystyrene sulfonate (Kayexalate® and generic brands), to investigate its possible interaction with other drugs. Similarly to the recently licenced drug patiromer (Veltassa®), sodium polystyrene sulfonate might bind to other medications, potentially decreasing their effects. To reduce this potential risk, prescribers and patients should consider separating dosing of sodium polystyrene sulfate from that of any other oral medications – both prescription and non-prescription drugs – by at least six hours. Health care professionals should monitor blood levels or clinical response to the other medications when appropriate.

► FDA Drug safety communication, 22 October 2015.

Iodine-containing contrast agents: hypoactive thyroid in infants
United States of America – The FDA has advised that rare cases of underactive thyroid have been reported in infants younger than 4 months following the use of contrast media containing iodine for X-rays and other medical imaging procedures. In all of the reported cases, the infants were either premature or had other serious underlying medical conditions. Available evidence suggests
that this is a rare effect that usually resolves without treatment or lasting effects. Manufacturers of affected products have been required to conduct a study to investigate this safety issue further.

Product information for all iodinated contrast media is being updated to include information about these cases. The FDA will continue to evaluate this issue.

► FDA Drug safety communication, 17 November 2015.

### Known risks

#### Magnesium oxide: hypermagnesaemia in older patients

**Japan** – The PMDA has warned that numerous cases of hypermagnesaemia have been reported in geriatric patients treated with magnesium oxide granules or tablets, with some serious outcomes even if the renal function was normal or if the dosage was below the recommended dose. In many cases, the hypermagnesaemia was only detected when serious outcomes such as loss of consciousness occurred.

Product information has been updated with advice that the medicine should be used with caution in geriatrics. Patients should be instructed to stop taking the medication and seek medical help immediately if they experience vomiting, bradycardia, muscular weakness, or somnolence. Patients should be carefully monitored with periodic measurement of serum magnesium concentration. For over-the-counter laxatives containing magnesium oxide, advice has been added to the package insert that elderly persons should consult a health professional before taking the product.

► PMDA Summary of investigation results and Revisions of precautions for prescription products, 20 October 2015.

► PMDA Summary of investigation results and Revisions of precautions for over-the-counter laxatives, 20 October 2015

#### Canagliflozin: decreased bone mineral density

**United States of America** – Based on updated information from several clinical trials the FDA has strengthened its warning about the increased risk of bone fractures in patients treated with the antidiabetic medicine canagliflozin (Invokana®, Invokamet®). Fractures can occur as early as 12 weeks after starting the drug. New information about the risk of decreased bone mineral density has been added to the section on adverse reactions in the product information. Health care professionals should consider factors that contribute to fracture risk before starting patients on canagliflozin.

The FDA is evaluating the risk of fractures with other SGLT2 inhibitors registered in the U.S., including dapagliflozin (Farxiga®, Xigduo XR®) and empagliflozin (Jardiance®, Glyxambi®, Synjardy®).

► FDA Drug safety announcement, 10 September 2015.

#### Mycophenolate: avoid exposure in pregnancy

**European Union** – The EMA has strengthened its warnings about exposure of pregnant women to the transplant medicine mycophenolate (CellCept® and other brand names) either by treatment with the medicine or through unprotected sex with a man taking the medicine. A
routine re-assessment of the benefits and
safety of mycophenolate has provided
updated evidence on the significant risk of
birth defects and spontaneous abortions.

Pregnant women should only be
exposed to mycophenolate if there is no
suitable alternative to prevent transplant
rejection. Mycophenolate can persist in
blood for six weeks after treatment, and
in sperm for 90 days after treatment.

Updated product information will
emphasize the need for contraception
with two effective methods during and
after treatment, pregnancy testing as
appropriate, and the need to avoid
donating blood or sperm during and after
treatment with mycophenolate.

► EMA Press release, 23 October 2015.

Ceftriaxone: acute generalised
exanthematous pustulosis
Japan – The PMDA has requested
updates to the product information to
ceftriaxone sodium hydrate to include the
risk of acute generalised exanthematous
pustulosis. This follows reports of this
adverse event in patients treated with
ceftriaxone sodium hydrate both in Japan
and overseas. A warning about this risk
is included in the product information
for ceftriaxone-containing medicines
approved in the European Union.

► PMDA Summary of investigation results and
Revision of precautions, 20 October 2015.

Roxithromycin: pseudo–
membranous colitis, cardiac effects
Japan – The PMDA has required
updates to the product information
for roxithromycin-containing
medicines to warn about the risks of
pseudomembranous colitis and of QT
interval prolongation and ventricular
tachycardia, including torsade de pointes.
This follows reports of these events in
Japan and elsewhere. Approved product
information in the European Union
includes warnings about these effects.

► PMDA Summary of investigation results and
Revision of precautions, 20 October 2015.

Strontium: cardiovascular risks
Canada – Health Canada has
implemented strengthened warnings
on cardiovascular risks associated with
products containing strontium citrate,
strontium gluconate or strontium lactate
with a daily dose of strontium between
4 mg and 682 mg, which are used to
help support bone mineral density.

These products are now limited to users
who have no history of heart disease,
circulatory problems or blood clots, or risk
factors for these conditions. A healthcare
professional should be consulted if the
product is used longer than six months.

This follows a Health Canada review
undertaken in light of findings in Europe
that led to restrictions for strontium
ranelate at strontium doses of 680 mg/
day. A Health Canada review of strontium
ranelate at daily doses below 680 mg/
and of non-ranelate forms of strontium
did not lead to firm conclusions. However,
Health Canada is using a precautionary
approach and considers that strontium-
containing medicines may potentially have
cardiovascular side effects in people who
are already at risk.

► Health Canada advisory, 22 October 2015.

Clozapine: severe neutropenia
United States of America – The
FDA has approved changes to
the requirements for monitoring,
prescribing, dispensing and receiving
the schizophrenia medicine clozapine, to address continuing safety concerns about severe neutropenia.

A new, shared risk evaluation and mitigation strategy (REMS), the so-called Clozapine REMS Program, replaces the separate clozapine registries maintained by individual manufacturers. In addition, neutropenia should now be monitored by the absolute neutrophil count (ANC) only, rather than in conjunction with the white blood cell count. Patients with benign ethnic neutropenia (BEN) are now also eligible for clozapine treatment. The ANC below which treatment should be interrupted in case of suspected clozapine-induced neutropenia has been lowered to 1,000 cells/mm³, and to 500 cells/mm³ for patients with BEN.

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**Dimethyl fumarate and other fumarate-containing medicines: new monitoring measures**

**European Union** – The EMA has issued advice in order to minimize the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with the multiple sclerosis medicine dimethyl fumarate (Tecfidera®). This follows reports of PML in patients that were not treated with any other medicines that may increase the risk of PML.

According to the new recommendations a complete blood count should be performed before starting treatment and every three months thereafter. Additionally, a baseline MRI should be provided. If during treatment the treatment lymphocyte counts drop to very low levels for more than six months, health professionals should consider stopping treatment. If treatment is continued, patients should be closely monitored.

Related recommendations have been issued for two fumarate-containing medicines used to treat psoriasis (Fumaderm® and Psorinovo®).

► EMA Press release, 23 October 2015.

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**Unchanged recommendations**

**Clopidogrel: no increased risk of death**

**United States of America** – The FDA has determined that long-term use of the antiplatelet drug clopidogrel (Plavix®) does not increase or decrease overall risk of death in patients with, or at risk for, heart disease. Neither did a review of clinical trials suggest that clopidogrel increases the risk of cancer or death from cancer. The FDA’s recommendations remain unchanged. Health care professionals should consider the benefits and risks of available antiplatelet medicines before starting treatment.

► FDA Drug safety announcement, 6 November 2015.

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**Human papillomavirus vaccines: benefits outweigh risks**

**European Union** – The EMA has completed a detailed scientific review of the evidence surrounding reports of two syndromes, complex regional pain syndrome and postural orthostatic tachycardia syndrome in young women given human papillomavirus (HPV) vaccines. This review concluded that the evidence does not support a causal link between the vaccines (Cervarix®, Gardasil/Silgard® and Gardasil-9®) and development of either of the two syndromes.
More than 80 million girls and women worldwide have received HPV vaccines to protect them from cervical cancer and various other cancers and conditions caused by HPV. The EMA has confirmed that the benefits of these vaccines therefore continue to outweigh their risks, and that no changes to the product information are necessary.


Entacapone: no clear evidence of cardiovascular events

United States of America – Following concerns about a possible increased risk of heart attacks, stroke or other cardiovascular events associated with entacapone (Comtan®) and with the combination of entacapone, carbidopa and levodopa (Stalevo®), an FDA review has found no clear evidence of such a risk associated with the use of the two medicines.

Entacapone-containing products are used to treat symptoms of Parkinson’s disease. In view of cardiovascular-related findings in clinical trials involving Stalevo®, the FDA had required the manufacturer to conduct an additional study, and had reviewed findings from this and another published study.

► FDA Drug safety communication, 26 October 2015.

Removal of class warnings

HIV medicines: class warnings about lipodystrophy and lactic acidosis removed

European Union – HIV medicines will no longer require a warning concerning lipodystrophy, i.e. fat redistribution, in their product information, and a number of nucleoside and nucleotide analogues will no longer require a warning about lactic acidosis.

Recent analyses show that only certain medicines cause fat changes, and that these fat changes concern lipoatrophy, i.e. the loss of subcutaneous fat. A specific warning related to lipoatrophy will remain in the product information for medicines containing zidovudine, stavudine and didanosine, and these medicines will also retain the lactic acidosis warning in line with current evidence.

► EMA Press release, 23 October 2015.

Safety reviews started

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<td>Treatment of upper airway infection</td>
<td>Serious allergic reactions including anaphylactic reactions</td>
<td>► EMA. Start of review of nasal and mouth sprays containing Fusafungine, 11 September 2015.</td>
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<td>Tramadol</td>
<td>Analgesic, not FDA-approved for use in children but being used off-label</td>
<td>Rare but serious risk of slow or difficult breathing in children aged 17 years and younger</td>
<td>► FDA Drug safety communication, 21 September 2015.</td>
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</tbody>
</table>
Packaging

Improved packaging for dementia treatments
United Kingdom – The MHRA is working with the pharmaceutical industry to optimize the presentation of medicines for Alzheimer’s disease. To help patients retain independence in taking their medicines, the days of the week will be indicated clearly on the blister packs. The change is expected to help improve patient confidence, safety and treatment outcomes. The improved packaging will be introduced from June 2016.

► MHRA Press release, 3 November 2015.

Medicines quality

Apotex: Canada import ban lifted, product re-testing imposed
Canada – Health Canada has lifted the import restrictions imposed in September 2014 on products from the Indian companies Apotex Pharmachem India Pvt. Ltd. (APIPL) and Apotex Research Private Limited (ARPL), and has imposed re-testing of products from the two sites at an Apotex good manufacturing practices-compliant facility in Canada and reporting of any deficient results. In September 2015, Health Canada inspectors started being present in Apotex’s Canadian facility to inspect the operations and the testing of the products from India.

In June 2015, Health Canada had inspected the corrective measures implemented at the Indian two sites and found that they have progressed in a satisfactory manner. Apotex Inc. has been requested to provide regular progress updates on the full and sustainable implementation of corrective actions at full production. Health Canada plans to re-inspect the sites in early 2016.

► Health Canada Advisory, 1 September 2015.

Dibotemin alfa-containing implant kit: suspended in Europe
European Union – The EMA has recommended the suspension of a kit for implant containing a powder, solvent and absorbable collagen sponge (Inductos®) due to manufacturing-related quality issues. This follows a review triggered by observations during inspection of the manufacturing site, located in the United States, by Dutch and Spanish authorities. Although there is no indication of risk to patients directly linked to the inspection findings, the suspension will remain in force until the issues are addressed.

The kit contains dibotemin alfa, a protein that helps with the formation of new bone tissue that grows into the sponge, which is gradually degraded by the body. Alternative treatments are available in the European Union.

► EMA Press release, 23 October 2015.
The following text is reproduced from the WHO Medical Product Alert No. 5/2015.

**Falsified emergency contraceptive circulating in East Africa**

This Medical Product Alert relates to the confirmed circulation of falsified versions of Postinor-2 (Levonorgestrel) in East Africa.

Postinor-2 is a widely used emergency contraceptive that should contain 0.75mg of levonorgestrel. The genuine product is manufactured by Gedeon Richter.

In August 2015, the Uganda National Drug Authority notified WHO of the seizure of falsified Postinor-2 discovered in Kampala, Uganda. All packs reported bear the same batch number and expiry/manufacturing dates.

The details of the product are as follows:
- **Product Name:** Postinor-2
- **Batch Number:** T38012
- **Manufacturing Date:** 08 2013
- **Expiry Date:** 08 2018

There is a non-useable, white “scratch area” on the reverse side of the pack. The packaging is in English, French and Spanish languages.

The batch number and manufacturing/expiry dates relate to a genuine batch of Postinor-2. Laboratory analysis has shown that the product contains zero active pharmaceutical ingredient. Furthermore, the manufacturers of genuine Postinor-2 have confirmed the packaging is falsified.

If you are in possession of the same batch of Postinor-2 shown in the below photograph and with a non-useable white “scratch area” on the reverse side of the pack please do not use, contact a Pharmacist or a Doctor as soon as possible for advice and report the incident to your National Medicines Regulatory Authority.

If you think you have taken this product, please seek medical advice immediately. If you have any information concerning the supply of this product please contact rapidalert@who.int

► [WHO. Medical Product Alert N° 5/2015, 18 November 2015 (includes photograph)](https://www.who.int)