Safety news

Safety warnings

**Brimonidine gel:**
**Systemic cardiovascular effects**
United Kingdom – The MHRA has informed health care professionals that systemic cardiovascular effects including bradycardia, hypotension and dizziness have been reported after application of brimonidine gel. Some patients required hospitalization. In approximately 30% of the cases most strongly suggestive of a cardiovascular effect, events occurred following application after laser therapy to the skin. To minimize the possibility of systemic absorption patients should be warned not to apply brimonidine gel to irritated or damaged skin, including after laser therapy to the skin.

According to the product information, dizziness was reported to occur uncommonly (with an estimated frequency of less than 10 in 1 000 patients treated), while hypotension and bradycardia were reported to occur rarely (in less than 1 of 1 000 patients treated). Brimonidine gel is indicated for the symptomatic treatment of rosacea in adults.

[MHRA Drug Safety Update volume 10 issue 11, June 2017](#).

**Lactose-containing injectable methylprednisolone:**
**Do not use in patients allergic to cow’s milk proteins**
European Union – The EMA has recommended against the use of injectable methylprednisolone containing lactose in patients with a known or suspected allergy to cow’s milk proteins. Patients being treated for an allergic reaction with methylprednisolone should have their treatment stopped if their symptoms worsen or if they develop new symptoms. The product information will be revised to reflect these recommendations, and the vials and packaging of these medicines will be clearly marked with a warning.

A review has found that lactose of bovine origin may introduce traces of cow’s milk proteins into the medicine which can trigger reactions in allergic patients. This may lead to additional doses being given, which will further worsen the patient’s condition. Considering that methylprednisolone is often used in emergency settings where details of patients’ allergies are not always known, the EMA recommended that cow’s milk proteins should be removed from the preparation. Companies have been asked to take steps by mid–2019 to replace current formulations with lactose-free ones.

[EMA. Article 31 referral. Medicinal products containing lactose of bovine origin for IV/IM use in acute allergic reactions. 7 July 2017](#).
[Health Canada Advisory, 6 September 2017](#).

**Amoxicillin:**
**Very rare risk of DRESS**
Ireland – The HPRA has informed health professionals that amoxicillin is associated with a very rare risk of drug reaction with eosinophilia and systemic symptoms (DRESS). The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) had reviewed a signal and had recommended that DRESS should
be added to the very rare severe cutaneous adverse reactions mentioned in the product information for amoxicillin-containing medicines.


**Azithromycin:**

**Acute generalized exanthematous pustulosis**

Japan – The regulatory authorities have recommended updates to the product information for azithromycin-containing products to include the risk of acute generalized exanthematous pustulosis (AGEP).(1)

A signal of this risk with azithromycin and three other macrolide antibacterials was also detected in the European Pharmacovigilance Issues Tracking Tool (EPITT) and is under assessment by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC).(2)

► (1) PMDA Summary of investigation results, 3 August 2017. PMDA. Revisions of precautions [webpage].


**Fluconazole, fosfluconazole:**

**Drug-induced hypersensitivity syndrome**

Japan – The PMDA has informed health professionals that cases of drug-induced hypersensitivity syndrome (also called Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with the antifungal medicine fluconazole both in Japan and overseas. The MHLW has recommended to add a warning about this risk to the product information for systemic products containing fluconazole or its pro-drug fosfluconazole. Initial symptoms of drug-induced hypersensitivity syndrome may include fever and rash, followed by serious delayed symptoms of hypersensitivity accompanied by liver function disorder, swollen lymph nodes, increased white blood cells, eosinophilia, and appearance of atypical lymphocytes. In case of such symptoms the medicine should be stopped and appropriate measures taken. This event is often accompanied by virus reactivation, and symptoms such as rash, fever, liver function disorder may persist or recur after treatment is stopped.

► PMDA Summary of investigation results, 4 July 2017. PMDA. Revisions of precautions [webpage].

**DAAs and warfarin:**

**INR changes**

New Zealand – Medsafe has advised health professionals to watch out for INR changes when direct-acting antivirals (DAAs) for hepatitis C (sofosbuvir, daclatasvir, asunaprevir, ledipasvir/sofosbuvir, elbasvir/grazoprevir and the combination products Viekira Pak® and Viekira Pak-RBV®) are used concomitantly with warfarin.

Recent evidence indicates that the use of DAAs together with warfarin may result in changes in international normalised ratio (INR). In most cases decreases in INR were reported. INR should be monitored frequently, and treatment adjusted as needed. Frequent monitoring of INR is also required in the post-treatment period, particularly if any warfarin dose adjustment has occurred.

Medsafe has further advised health professionals to use available tools to check for drug interactions with DAAs, and has reminded them that the overall benefit-risk balance of DAA regimens remains positive.(1)
A signal was under assessment by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) in 2016 and product information was updated in the EU. (2)

2. EMA. PRAC recommendations on signals, 15 September 2016.

Bendamustine:
Risk of opportunistic infections greater than expected
United Kingdom – The MHRA has alerted health professionals that the risk of opportunistic infections for all patients receiving the cancer medicine bendamustine (Levact®), including those receiving off-label treatment, may be greater than previously recognized.

Increased mortality was seen in clinical trials when bendamustine was used in combination treatments outside its approved indications, which include treatment of chronic lymphocytic leukaemia, non-Hodgkin’s lymphoma and multiple myeloma in certain patients. Hepatitis B virus (HBV) reactivation has also been reported. Patients should be advised to report promptly any new signs of infection and should be monitored for opportunistic infections as well as cardiac, neurological, and respiratory adverse events.


Nivolumab:
Sclerosing cholangitis
Japan – The PMDA has informed health professionals about cases of sclerosing cholangitis reported in patients treated with the cancer medicine nivolumab (Opdivo®) in Japan. Sclerosing cholangitis is characterized by swelling, inflammation, scarring and destruction of the bile ducts inside and outside of the liver. The product information for nivolumab in Japan will be updated to include a warning about this risk.

1. PMDA Summary of investigation results, 4 July 2017. PMDA. Revisions of precautions [webpage].

Nivolumab, pembrolizumab:
Organ transplant rejection
United Kingdom – The MHRA has informed health professionals that since November 2016 nine cases of rejection of solid organ transplants, including renal and corneal grafts, have been reported in the post-marketing setting in cancer patients treated with the monoclonal antibodies nivolumab (Opdivo®) or pembrolizumab (Keytruda®) in the EU. In two cases the adverse events occurred in association with ipilimumab (Yervoy®), which carries a warning that it may interfere with immunosuppressive therapy, resulting in an increased risk of graft rejection.

Health professionals have been advised to consider the benefits of treatment with these medicines against the risk of possible organ transplant rejection for each patient.


Pembrolizumab: myeloma clinical trials halted after patient deaths
United States of America – Based on data from two recently halted clinical trials with the anti-cancer medicine pembrolizumab (Keytruda®), the FDA has warned about the risk of increased mortality with this medicine when used in combination with dexamethasone and an immunomodulatory agent (lenalidomide or pomalidomide) for the treatment of patients
with multiple myeloma. Other multiple myeloma clinical trials of pembrolizumab, other PD-1/PD-L1 cancer medicines and other combinations are currently undergoing clinical evaluation.

Pembrolizumab is not approved for treatment of multiple myeloma. The medicine can continue to be used for approved indications, which in the U.S. include melanoma, lung cancer, head and neck cancer, classical Hodgkin lymphoma, urothelial carcinoma and microsatellite instability-high (MSI-H) cancer.


Statement from CDER Director, 31 August 2017.

Atezolizumab:
Severe cases of myocarditis

New Zealand – The marketing authorization holder, in consultation with Medsafe, has informed health professionals that cases of myocarditis have been reported in clinical trials with the cancer medicine atezolizumab (Tecentriq®). Atezolizumab should be withheld for Grade 2 myocarditis, initiation of treatment with systemic corticosteroids may be considered. Atezolizumab should be permanently discontinued for Grade 3 or 4 myocarditis.

Immune-mediated myocarditis is listed in the data sheets of similar-in-class medicines. The data sheet for atezolizumab will be updated to reflect this risk.

► Medsafe Safety Information, 3 August 2017.

Ibrutinib:
Cardiac arrhythmia, hepatitis B reactivation, opportunistic infections

United Kingdom – The MHRA has alerted health care professionals to new safety issues with the blood cancer medicine ibrutinib (Imbruvica®) that were identified in a routine European review of the safety profile of ibrutinib in the pre- and post-marketing settings.

Cases of ventricular tachyarrhythmia have been reported in patients treated with ibrutinib. Treatment should be interrupted in patients who develop symptoms such as palpitations, chest pain, dyspnoea, dizziness or fainting. Treatment should only be restarted after the benefit-risk balance has been assessed and found favourable.

Cases of hepatitis B (HBV) reactivation have been reported with ibrutinib. Patients should be tested for HBV infection before treatment initiation. In case of a positive hepatitis B serology a liver disease expert should be consulted, and if treatment with ibrutinib is found necessary patients should be monitored and managed to prevent HBV reactivation.

Opportunistic infections are a known, very common adverse event in patients treated with ibrutinib. Given the relatively high number of fatal cases, healthcare professionals should consider prophylaxis according to standard of care for patients who are at an increased risk of opportunistic infections.

► Drug Safety Update volume 11 issue 1, August 2017: 1

Daclizumab:
Risk of serious liver injury, restrictions

European Union – The EMA is provisionally restricting the use of daclizumab (Zinbryta®) because of the risk of severe liver injury. The medicine should only be used in patients with highly active relapsing multiple sclerosis that has failed to respond to certain other treatment, and to patients with rapidly evolving relapsing disease who cannot be treated with other medicines. Patients with liver injury must not be given
daclizumab, and caution should be used when prescribing it together with medicines that can damage the liver. Treatment should not be initiated in patients with autoimmune diseases other than multiple sclerosis. Health professionals should monitor the liver function of patients treated with daclizumab and watch them closely for signs and symptoms of liver injury.

An EU-wide safety review of daclizumab is ongoing. It was triggered following the death from fulminant liver failure of a patient in an observational study as well as four cases of serious liver injury. The risk of liver damage was known at the time when daclizumab was approved in the EU, and several measures were recommended to manage this risk.

Loxoprofen topical preparations: Shock, anaphylaxis

Japan, Korea – Cases of shock and anaphylaxis have been reported in patients treated in Japan with topical formulations of loxoprofen, a nonsteroidal anti-inflammatory drug (NSAID). A warning about this risk will be included in the product information for loxoprofen-containing gels, sprays, tapes and other preparations approved in Japan. Patients should be carefully monitored; in case of any symptoms such as decreased blood pressure, urticaria, laryngeal oedema or dyspnoea loxoprofen should be stopped immediately and appropriate measures should be taken. A similar update is in preparation for loxoprofen-containing products approved in the Republic of Korea.

Gabapentin:

Respiratory depression without concomitant opioid use

Ireland – The HPRA has warned health professionals that in rare cases gabapentin can cause severe respiratory depression even without concomitant opioid use. Dosage adjustments should be considered, especially in patients with risk factors such as the use of CNS depressant medication, compromised breathing function,

Denosumab:

Osteonecrosis of the outer ear canal

European Union – The approved product information for denosumab (Prolia®, Xgeva®) has been revised to include a warning on the risk of osteonecrosis of external auditory canal. Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment. The warning was added as an outcome of the periodic safety update assessment concluded on 27 June 2017.

The MHRA has informed health professionals in the U.K. of the update to the product information of denosumab. In December 2015 the MHRA had published a Drug Safety Update article about very rare reports of osteonecrosis of the external auditory canal with bisphosphonates, which are – like denosumab – known to be associated with osteonecrosis of the jaw. For all these medicines, the risk of osteonecrosis at other sites of the body continues to be kept under close review.

Gabapentin:
respiratory or neurological disease, renal impairment and age.\(^{(1)}\)

The warning follows a review by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC), which recommended that the product information for gabapentin should be updated to reflect this risk.\(^{(2)}\)


EMRA. PRAC recommendations on signals. Adopted at the 6-9 June 2017 PRAC meeting. 22 June 2017.

Hydroxocobalamin antidote kit: Acute kidney injury

Japan – The PMDA has reviewed information related to reports of acute kidney injury reported in patients receiving hydroxocobalamin as treatment for cyanogen and cyanide poisoning both in Japan and overseas. Cases of renal tubular necrosis have also been reported. The MHLW has recommended an update to the product information for the hydroxocobalamin kit (Cyanokit\(^{®}\)), advising health professionals to monitor patients carefully for signs of this adverse event.

► PMDA Summary of investigation results, 4 July 2017.

PMDA. Revisions of precautions [webpage].

Diagnostics

Hightop HIV home testing kits: Unreliable results

United Kingdom – The MHRA has informed the public that it has seized more than 100 unreliable HIV home-testing kits and is investigating a number of kits that may be unreliable and may provide false results. The affected kit is the Hightop HIV/AIDS Home Test Kit. The kits, manufactured by Qingdao Hightop Biotech Co Ltd, do not have a valid CE mark, meaning that the product has not undergone the regulatory assessments required for the EU market. All sales of the product into the U.K. market have been stopped by the manufacturer.


Known risks

Warfarin: Calciphylaxis

Japan – The MHLW, upon advice from the PMDA, has required updates to the product information for warfarin to warn about the risk of calciphylaxis.\(^{(1)}\)

In the EU, product information for warfarin was amended in 2016 to include a warning about this risk. Calciphylaxis is a very rare but serious condition that causes vascular calcification and cutaneous necrosis, and is most commonly observed in patients with known risk factors such as end-stage renal disease. Cases have been reported in patients taking warfarin, including those with normal renal function, and evidence suggests that on rare occasions warfarin use might lead to calciphylaxis. If calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.\(^{(2, 3)}\)

► (1) PMDA Summary of investigation results, 3 August 2017.

PMDA. Revisions of precautions [webpage].

(2) PRAC recommendations on signals. EMA/PRAC/313187/2016. 26 May 2016.


Local corticosteroids: Central serous chorioretinopathy

United Kingdom – The MHRA has advised health professionals that patients treated with both systemic or local corticosteroids
should be asked to report any blurred vision or other visual disturbances. Referral to an ophthalmologist should be considered to establish the cause of the vision problems.

Treatment with systemic corticosteroids is a known risk factor for central serous chorioretinopathy (CSCR), an accumulation of subretinal fluid that can ultimately cause retinal detachment. CSCR has also been listed as a rare side effect with all locally administered corticosteroid formulations. Although the causes of blurred vision are various, CSCR should be considered as a possible cause in patients treated with corticosteroids, including those administered through local routes.

► Drug Safety Update volume 11 issue 1, August 2017: 2.

**Hydroquinone skin lighteners:**
**Skin damage; environmental damage**

Canada – Health Canada will be changing the prescription status of skin-lightening products containing hydroquinone at concentrations greater than 2%. These products will be available by prescription only as of August 2018, due to their risks for the skin and for the environment. A transition plan was developed following an online consultation with stakeholders.

Skin lighteners containing more than 2% hydroquinone can cause severe skin redness, burning or stinging, dryness or cracking of the skin, blisters or oozing, or skin discolouration. They can also cause cancer in laboratory animals, and potentially in humans.


**Review outcomes**

**E. coli probiotic:**
**Use in irritable bowel syndrome only**

European Union – At the request of the German regulatory authority the EMA has reviewed a probiotic containing *Escherichia coli* bacteria (Symbioflor 2* and associated names) and has concluded that it can continue to be used for irritable bowel syndrome in adults. Benefit has not yet been established in children. The medicine should no longer be used for other functional gastrointestinal disorders as there are insufficient data to support this use.

The product information will be updated in line with this review. The marketing authorization holder has been requested to submit results of a well-designed study to national authorities demonstrating the medicine's efficacy for treating different variants of irritable bowel syndrome, as a condition for continued marketing.

► EMA Press release, 23 June 2017.
EMA Article 31 referrals. Symbioflor 2.

**Modified-release paracetamol:**
**To be removed from market**

European Union – The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the marketing authorizations of modified- or prolonged-release release paracetamol should be suspended. The decision was taken in view of the difficulties of managing overdose in patients.

Although modified-release paracetamol tablets have acceptable benefits and risks when used in the approved way, experience has shown that in overdose the treatment procedures – which were developed for
immediate-release paracetamol – are not appropriate.
► EMA News, 1 September 2017.

**Gadolinium-based contrast agents: Restrictions maintained**

**European Union** – The EMA has confirmed its recommendations to restrict the use of some intravenous linear gadolinium agents used in MRI body scans and to suspend the authorizations of others. Macrocyclic gadolinium agents can continue to be used, but only at the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable.

**Australia** – The TGA has reviewed recent information on gadolinium-based contrast agents and is working with marketing authorization holders to update the relevant product information. Health professionals were advised to use gadolinium-based contrast agents only where necessary, to use the lowest effective dose, to carefully consider the choice of agent, and to avoid repetitive scans using these contrast agents unless deemed clinically necessary.

**New Zealand** – Medsafe and its Medicines Adverse Reactions Committee (MARC) considered that use of gadolinium based contrast agents should be restricted to situations where they are expected to provide additional information allowing the patient’s condition to be diagnosed or monitored correctly.
► Medsafe Alert communication, 21 August 2017.

**Non-compliance with good practices**

**Dr Reddy’s Laboratories**

German regulators have issued a statement of non-compliance with good manufacturing practices (GMP) for Dr. Reddy’s Laboratories Ltd’s manufacturing site located in Qutubullapur Mandal, Ranga Reddy District, Bachupally Village. In an inspection conducted on 1st August 2017 critical deficiencies were observed including systematic invalidation of out-of-specification results in hundreds of cases, the systematic failure of systems to document and report discrepancies, non-conformances, incidents and unusual events, and false confirmation of successful cleaning of rooms and equipment.

The German regulators issued a rapid alert concerning the products on the German market and proposed an EU-wide import stop until successful re-inspection of the site.

**Hetero Labs Limited**

The FDA has issued a warning letter to Hetero Labs Limited over non-compliance with GMP at its Unit V facility at Polepally Village, Jadcherla Mandal in Telangana, India. This follows an inspection of the site conducted on 7-16 December 2016, during which deficiencies were observed with regard to investigation of out-of-specification testing results, cleaning, written procedures for quality control, and in-process controls. The company has been given 15 days to respond, specifying the corrective actions taken to remedy the shortcomings and prevent their recurrence.
**Falsified product alerts**

**Quinine sulfate (Africa)**
The WHO Medical Product Alert No. 2/2017 relates to the circulation of two confirmed falsified versions of quinine sulfate in the Democratic Republic of the Congo. The two products contain zero active pharmaceutical ingredient.

Quinine sulphate is used for the treatment of P. falciparum malaria in the region. In April 2017, a local non-governmental organization (NGO) discovered the falsified products in pharmacies in the north-east of the Democratic Republic of the Congo. The products were submitted to a WHO-prequalified laboratory for testing. The analysis showed that neither of the two products contained any of the stated active pharmaceutical ingredient. The details on the product labels are shown below.

<table>
<thead>
<tr>
<th>Product 1</th>
<th>Product 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product name: Quinine sulphate 300</td>
<td>Quinine bisulphate 300mg. B.P.</td>
</tr>
<tr>
<td>Batch number: 15946</td>
<td>7422</td>
</tr>
<tr>
<td>Expiry date: 03/18</td>
<td>12-2018</td>
</tr>
<tr>
<td>Manufacturing date: 02/15</td>
<td>5-2015</td>
</tr>
<tr>
<td>Manufacturer name stated on the label: Remedica</td>
<td>Laboratory &amp; Allied Ltd</td>
</tr>
</tbody>
</table>

The manufacturers indicated on the label of the two products, Remedica and Laboratory & Allied Ltd, have stated that they did not manufacture these specific products. The product details shown above do not correspond to the genuine manufacturer records.

► WHO Medical Product Alert No. 2/2017 (includes photographs).

Report suspected falsified products to the competent national regulatory authority and/or pharmacovigilance centre, and notify WHO at rapidalert@who.int.

**Cancer medicines (East Africa)**
The WHO Medical Product Alert No. 3/2017 relates to falsified Avastin (bevacizumab) and Sutent (sunitinib malate) circulating in East Africa. The two falsified medicines were discovered and seized by the National Drug Authority of Uganda in July 2017 and reported to WHO. Both products were being distributed in the vicinity of various cancer treatment centres in Kampala, Uganda.

The genuine manufacturers of both products have confirmed that they did not manufacture these products. Avastin* is the trade name of a medicine manufactured by Roche/Genentech for the treatment of various cancers. Sutent* is the trade name of a
Falsified product alerts

medicine for the treatment of pancreatic cancer manufactured by Pfizer. Neither of the two products is manufactured by AstraZeneca as shown on the falsified versions.

These falsified versions of Avastin® and Sutent® are being presented in plastic bottles containing blue/grey tablets. The genuine version of Avastin® is supplied only as an injection for intravenous use. Genuine Sutent® is only available as gelatin capsules.

Details of the falsified products are as follows:

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Batch Number</th>
<th>Expiry Date</th>
<th>Manufacturer Name Stated on Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin</td>
<td>NC2001</td>
<td>2-2019</td>
<td>AstraZeneca and AstraZenaca</td>
</tr>
<tr>
<td>Sutent</td>
<td></td>
<td></td>
<td>AstraZeneca and AstraZenaca</td>
</tr>
</tbody>
</table>

WHO Medical Product Alert No. 3/2017. (includes photographs)

Report suspected falsified products to the competent national regulatory authority and/or pharmacovigilance centre, and notify WHO at rapidalert@who.int.

Counterfeit packs of schizophrenia medicine (Germany, Denmark)

German and Danish parallel importers and the Danish Medicines Agency have withdrawn a total of four batches of the schizophrenia medicine paliperidone palmitate (Xeplion®) 150 mg from wholesale distributors, hospitals and pharmacies, because the batches contained counterfeit packs.

An analysis of the counterfeit packs from two of the affected batches by the manufacturer of the genuine product, Janssen, has shown that the outer packaging has been falsified, but the syringe and its content as well as the enclosed needles are authentic products from Janssen, and no signs were found that syringes and needles have been tampered with. The Danish Medicines Agency therefore considers that the risk for patients is low.

However, it cannot be ruled out that the counterfeit packs have been handled improperly since they were packed and handled outside the legal chain. A risk of falsification has been identified in additional batches, which have been quarantined. The Danish Medicines Agency continues to investigate the matter in collaboration with the European Medicines Agency and the regulators of the other affected countries.