Safety news

Safety warnings

Miconazole oral gel:
Do not use in patients taking warfarin
United Kingdom – The MHRA has warned that patients taking warfarin should not use over-the-counter miconazole oral antifungal gel. This follows reports of bleeding events, some with fatal outcome, in such patients. If miconazole oral gel must be used with an oral anticoagulant such as warfarin, patients should be monitored carefully, and the anticoagulant effect titrated carefully. Patients who experience sudden unexplained bruising, nosebleeds or blood in the urine should stop using miconazole and seek immediate medical attention.

A contraindication, and more prominent warnings about this risk, will be included in the product information and on the packaging for miconazole oral gel.


Obeticholic acid:
Serious liver injury
United States of America – The FDA has warned that obeticholic acid (Ocaliva®) is being dosed incorrectly in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death. Obeticholic acid may also be associated with liver injury in some patients with mild disease who are receiving the correct dose.

Patient's baseline liver function should be determined before treatment is initiated. Patients with moderate to severe liver impairment (Child-Pugh B and C) should receive a dose of 5 mg once weekly, which can be increased up to a maximum of 10 mg twice weekly if needed. All patients treated with obeticholic acid should be monitored frequently, and the dosing frequency reduced to once- or twice-weekly for patients who progress to moderate or severe liver impairment. If liver injury is suspected, obeticholic acid should be stopped, and should only be started again after the patient has stabilized and if the benefits outweigh the risks. Patients should be educated on the symptoms of potential liver injury.

Obeticholic acid is used to treat primary biliary cholangitis, a rare, chronic disease that causes the bile ducts in the liver to become inflamed and destroyed, resulting in a build-up of bile in the liver which eventually loses its ability to function.


Linagliptine:
Interstitial pneumonia
Japan – The PMDA has recommended that the product information for the antidiabetic medicine linagliptine should be updated to reflect the risk of interstitial pneumonia. This follows reports of this adverse event observed in patients treated with linagliptin in Japan. The revised product information states that if signs and symptoms such as cough, dyspnoea, fever and abnormal chest sounds are observed, chest X-ray, chest CT scan and serum marker tests should be performed immediately. If interstitial pneumonia is suspected, the medicine
should be discontinued and appropriate measures taken, including administration of corticosteroids.

► PMDA Summary of investigation results and MHLW Revision of precautions, 17 October 2017.

**Dabigatran:**
**Liver toxicity**

Japan – The PMDA has informed health professionals that cases of acute liver failure, liver function disorder and jaundice have been reported in patients treated with the antithrombotic medicine dabigatran (Pradaxa®) in Japan. The MHLW has recommended to add a warning to the product information, stating that patients should be monitored, and in case of abnormalities dabigatran should be stopped and appropriate measures taken.

► PMDA Summary of investigation results and MHLW Revision of precautions, 12 September 2017.

**Flucloxacillin:**
**Metabolic acidosis**

Ireland – The HPRA has informed healthcare professionals that flucloxacillin, when used together with paracetamol, has been associated with very rare cases of high anion gap metabolic acidosis (HAGMA). Patients with severe renal impairment, sepsis or malnutrition might be at higher risk of this adverse event, especially if they are taking the maximum daily doses of paracetamol.

The warning follows a review by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC), which advised that the product information should be updated to reflect this risk.


**Epoetins:**
**Severe skin reactions**

Ireland – The Marketing Authorisation Holders (MAHs) of all epoetins available in Ireland, in agreement with EMA and HPRA, have warned health professionals that severe skin reactions, including some fatal ones, have been reported with epoetins in the post-marketing setting.

A detailed analysis of all available information revealed that severe skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can be considered to be a class effect of epoetins. More severe reactions were reported with long-acting epoetins. The frequency of these reactions could not be calculated, but they appear to occur very rarely.

Patients should be instructed to contact their doctor immediately and stop epoetin treatment if they experience any signs or symptoms of a severe skin reaction. Patients who have developed such reactions due to the use of an epoetin must never be given an epoetin again.

The product information of all epoetin-containing products is being updated to reflect these warnings.


**Intraocular vancomycin:**
**Potentially blinding complications**

United States of America – Many ophthalmologists use intraocular vancomycin during cataract surgery to prevent postoperative endophthalmitis. The FDA has informed health professionals that haemorrhagic occlusive retinal vasculitis (HORV) has been observed in dozens of patients after injections of vancomycin into the eye at the end of
otherwise uncomplicated cataract surgeries. HORV is a newly described, rare, potentially blinding postoperative complication.

The FDA has recommended against the prophylactic use of intraocular vancomycin, alone or with other active ingredients, during cataract surgery.

There is no FDA-approved intraocular vancomycin formulation. The injection is usually prepared on site or obtained from a compounding pharmacy. A warning has been added to the product information of vancomycin injection, stating that the safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established, and that vancomycin is not indicated for prophylaxis of endophthalmitis.


Fingolimod: Contraindicated in patients with heart conditions

Ireland – The marketing authorization holder, in agreement with EMA and HPRA, has informed healthcare professionals that fingolimod is now contraindicated in patients with myocardial infarction, unstable angina pectoris, stroke, transient ischaemic attacks, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure in the previous 6 months. It is also contraindicated in patients with severe cardiac arrhythmias requiring treatment with certain anti-arrhythmic drugs, patients with second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block or sick sinus syndrome that do not wear a pacemaker, and patients with a baseline QTc interval ≥500 milliseconds.

Fingolimod is used to treat multiple sclerosis. Its risk of serious cardiac rhythm disturbances is described in the product information. However, serious adverse events including fatalities have been reported. The contraindications have been introduced to minimize the risk of severe adverse events in patients with cardiac conditions. The warnings and precautions on the immunosuppressive effect of fingolimod potentially leading to serious infections and cancer are also being updated.

► HPRA. Third party publication, posted 7 November 2017.

Daclizumab: Serious liver damage, further restrictions

European Union – The EMA has recommended further restrictions on the use of the multiple sclerosis medicine daclizumab (Zinbryta*), as an update to the provisional measures introduced in July 2017. A review has found that unpredictable and potentially fatal immune-mediated liver injury can occur during treatment with daclizumab and for up to six months thereafter. Warnings will be added to the product information, and patients and healthcare professionals in the EU will need to sign a form to confirm that they have discussed this risk.

Daclizumab should only be used to treat relapsing forms of multiple sclerosis in patients who have had an inadequate response to at least two disease-modifying therapies (DMTs) and cannot be treated with other DMTs. Daclizumab must not be used in patients with pre-existing liver disease and should not be started in new patients with over two times the upper normal limit
of liver enzymes. It is recommended that daclizumab should not be used in patients with other autoimmune conditions.

Patients’ liver function (ALT, AST and bilirubin) should be monitored closely at least once a month before each treatment and for up to six months after treatments have stopped. Patients with liver enzyme levels over three times the upper normal limit should stop taking daclizumab. Patients with signs or symptoms of liver damage and those who test positive for hepatitis B or C infection should be referred to a specialist. If a patient does not comply with monitoring requirements or if the response to treatment is inadequate, treatment discontinuation should be considered.


**Levetiracetam:**
**Neuroleptic malignant syndrome**

*Japan* – Following cases of neuroleptic malignant syndrome reported in patients treated with the antiepileptic medicine levetiracetam (Keppra®) in Japan, the PMDA has recommended that the product information should be updated to include information about this risk. Patients treated with levetiracetam should be carefully monitored for signs and symptoms such as fever, muscle rigidity, increased creatinine kinase, tachycardia, blood pressure changes, disturbed consciousness, sweating and increased white blood cells. If neuroleptic malignant syndrome occurs treatment should be discontinued and appropriate measures taken such as cooling of the body, hydration and respiratory management. Decreased renal function with myoglobinuria may also occur in patients treated with levetiracetam.

► PMDA Summary of investigation results and MHLW Revision of precautions, 17 October 2017.

**Sodium polystyrene sulfonate:**
**Separate dosing from other oral medicines**

*United States of America* – The FDA has recommended that the potassium-lowering medicine sodium polystyrene sulfonate (Kayexalate® and related names) should be taken at least 3 hours before or after any other prescription or over-the-counter medicines taken by mouth. That time should be increased to 6 hours for patients with gastroparesis or other conditions resulting in delayed emptying of food from the stomach into the small intestine.

In October 2015 the FDA had requested manufacturers to conduct additional drug interaction studies on sodium polystyrene sulfonate. An *in vitro* study has confirmed that it binds to many commonly prescribed oral medicines, decreasing their absorption and therefore their effectiveness. The product information for medicines containing sodium polystyrene sulfonate is being updated.


**Radium-223 dichloride:**
**Do not use with abiraterone and prednisone or prednisolone**

*European Union* – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has warned health professionals against the use of the prostate cancer medicine radium-223 dichloride (Xofigo®) in combination with abiraterone (Zytiga®) and prednisone or prednisolone.

This warning follows findings of an increased risk of death and fractures in an ongoing clinical trial. Treatment with Radium-223 dichloride has been stopped
in the trial, and all the patients involved are being monitored closely. The PRAC has started a review of the product.
► EMA News, 1 December 2017.

Known risks

Amoxicillin:
Thrombocytopenia
Japan – Following reported cases of thrombocytopenia observed in patients treated with amoxicillin-containing products in Japan, the PMDA has recommended that a warning about this potential adverse effect should be added to the product information. Reversible thrombocytopenia is also listed as a very rare adverse event in the product information for some amoxicillin-containing products approved in the EU.
► PMDA Summary of investigation results, 17 October 2017.

Moxifloxacin:
Rhabdomyolysis
Japan – The PMDA has recommended to update the product information for moxifloxacin-containing products to include the risk of rhabdomyolysis. Patients should be monitored, and treatment should be stopped and appropriate measures taken if signs and symptoms of rhabdomyolysis are observed. Health professionals should also be alert to the potential onset of acute kidney injury due to rhabdomyolysis.

The product information for moxifloxacin-containing products approved in the UK states that rhabdomyolysis has been reported very rarely with other fluoroquinolone antibiotics and might possibly also occur during treatment with moxifloxacin.
► PMDA Summary of investigation results and MHLW Revision of precautions, 17 October 2017.

Palivizumab:
Thrombocytopenia
Japan – Following reported cases of thrombocytopenia with the immunoglobulin palivizumab (Synagis®) in Japan, the PMDA has recommended that the product information should be updated. Palivizumab is approved in Japan to prevent serious lower respiratory tract infection caused by RSV (respiratory syncytial virus) in neonates and infants. The EU-approved product information includes thrombocytopenia as an uncommon adverse event identified from post-marketing surveillance.
► PMDA Summary of investigation results and MHLW Revision of precautions, 12 September 2017.

Cladribine:
Progressive multifocal leukoencephalopathy
Ireland – The marketing authorization holder, in agreement with EMA and HPRA, has informed healthcare professionals that cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with cladribine (Litak®).

Cladribine is an anti-cancer medicine that can induce myelosuppression and immunosuppression, as well as lymphopenia. It can therefore increase the risk of PML, a rare, potentially fatal demyelinating disease of the brain caused by reactivation of the JC virus. Cladribine is also authorized in Ireland for the treatment of highly active relapsing multiple sclerosis. The product information for this indication already includes a warning about the risk of PML.
► Direct healthcare professional communication, 1 December 2017.
Clozapine:
Fast-onset intestinal obstruction
United Kingdom – The MHRA has reminded healthcare professionals of the risk of fast-onset intestinal obstruction, faecal impaction and paralytic ileus associated with clozapine. The adverse effects range from constipation, which is very common, to very rare but serious and potentially fatal events. Particular care should be taken in patients receiving other medicines known to cause constipation, those with a history of colonic disease or lower abdominal surgery, and patients aged 60 years and older. Clozapine is contraindicated in patients with paralytic ileus. Patients should be advised to report constipation immediately. It is vital that constipation is recognized early and actively treated.

The risk of impaired intestinal movement is long established with clozapine; however, health care professionals may not be sufficiently aware of this risk and its potential fast onset.

► Drug Safety Update volume 11, issue 3; October 2017: 4.

Buprenorphine, methadone:
Manage risks in opioid-dependent patients taking benzodiazepines
United States of America – The FDA has advised that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other central nervous system depressants. Although the combined use of these medicines increases the risk of serious side effects (including overdose and death), the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce the risks of serious adverse effects. The product information for buprenorphine and methadone will be updated accordingly, and detailed recommendations will be included on minimizing the combined use of medication-assisted treatment and benzodiazepines.


Review outcomes

Factor VIII medicines
European Union – The EMA has concluded that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between factor VIII medicines derived from plasma and those made by recombinant DNA technology.

The risk of inhibitor development will continue to be assessed individually for each product, regardless of class, as more evidence becomes available. The prescribing information of factor VIII medicines will be updated to include, as appropriate, inhibitor development as an adverse effect that is very common in previously untreated patients and uncommon in previously treated patients, and to state that low levels of inhibitors pose less risk of severe bleeding than high levels.

► EMA. Factor VIII medicines: no clear and consistent evidence of difference in risk of inhibitor development between classes. 15 September 2017.
## Reviews started

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Use</th>
<th>Concerns</th>
<th>Reviewing authority reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyethyl starch</td>
<td>Management of hypovolaemia</td>
<td>Restrictions were introduced in the EU in 2013 to reduce risks of kidney injury and death. However, the restrictions are not being adhered to.</td>
<td>EMA Press release, 27 October 2017.</td>
</tr>
<tr>
<td>Ulipristal (Esmya*)</td>
<td>Treatment of uterine fibroids</td>
<td>Four reports of serious liver injury, three of which ended in liver transplantation. Note: Ulipristal acetate is also the active substance of a single-dose emergency contraceptive, ellaOne*. There are no concerns with ellaOne* at this time.</td>
<td>EMA, Esmya Article-20 procedure – Review started, 1 December 2017.</td>
</tr>
<tr>
<td>Febuxostat</td>
<td>Treatment of gout</td>
<td>Preliminary results from a safety clinical trial show an increased risk of heart-related death, and death of all causes, with febuxostat compared to allopurinol.</td>
<td>FDA Drug safety communication, 15 November 2017.</td>
</tr>
<tr>
<td>Radium-223 (Xofigo*)</td>
<td>Treatment of metastatic castration-resistant prostate cancer</td>
<td>Increased risk of death and fractures reported in an ongoing clinical trial. While a full investigation is ongoing, doctors in the EU have been advised not to use radium-223 in combination with abiraterone (Zytiga*) and prednisone/prednisolone.</td>
<td>EMA, Xofigo Article-20 procedure – Review started, 1 December 2017.</td>
</tr>
</tbody>
</table>
Non-compliance with good practices

**Lupin Ltd.**
United States of America – The FDA has sent a warning letter to Lupin Ltd following observations of non-compliance with good manufacturing practice (GMP) at the company’s Goa and Indore sites. During FDA inspections of the sites conducted in May 2017 various deficiencies were observed, including inadequate handling of out-of-specification results in production. The deficiencies were not adequately addressed by the manufacturer’s corrective and preventive action. The FDA had found similar shortcomings at the two sites during earlier inspections in 2015 and 2016. The company was requested to immediately and comprehensively assess its global manufacturing operations.


Falsified medicines

**Falsified Penicillin V circulating in Cameroon**
The WHO Medical Product Alert No. 4/2017 relates to the circulation of falsified Penicillin V (phenoxyethylpenicillin) circulating in Cameroon.

Phenoxyethylpenicillin is used to treat particular bacterial infections and is listed as a WHO Essential Medicine and key antibiotic. In September 2017, an NGO identified a product labelled as Pencillin-V Tablets being sold at a street market in the south-west region of Cameroon. Product details are shown below

<table>
<thead>
<tr>
<th>Product name:</th>
<th>PENICILLIN-V TABLETS</th>
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<tr>
<td>Batch number:</td>
<td>190</td>
</tr>
<tr>
<td>Expiry date:</td>
<td>Oct 2019</td>
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<tr>
<td>Manufacturing date:</td>
<td>April 2015</td>
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<tr>
<td>Stated active pharmaceutical ingredient:</td>
<td>Phenoxyethylpenicillin (with spelling error)</td>
</tr>
<tr>
<td>Manufacturer name stated on the label:</td>
<td>OXFORD PHARMA CO. LTD, BELGIUM</td>
</tr>
</tbody>
</table>

Further investigation has revealed the following:

- The stated manufacturer does not exist in Belgium. The label contains spelling mistakes and inaccuracies such as the strength/composition.
- Laboratory analysis indicates that the tablets do not contain any phenoxyethylpenicillin. Instead each tablet contains 50 mg of paracetamol. The paracetamol content is sufficient to reduce fever if the tablets are taken according to the label directions. This may deceive patients and healthcare professionals into believing that this product is effective, and delay the seeking of an appropriate treatment for the infection. There have been no known adverse reactions reported to WHO at this stage.

► WHO Medical Product Alert No. 4/2017 (includes photographs).

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