Safety news

Safety warnings

**DPP-4 inhibitors: Pemphigoid**

*Japan* – A warning about the risk of pemphigoid has been added to the approved product information in Japan for antidiabetics containing the dipeptidyl peptidase 4 (DPP-4) inhibitors alogliptin, linagliptin or teneligliptin. Health professionals are advised to refer patients with blisters, erosions or other signs or symptoms of this skin condition to a dermatologist, and to consider treatment discontinuation.

► *PMDA Summary of investigation results and MHLW Revision of precautions, 22 November 2016.*

**Polaprezinc: copper deficiency**

*Japan* – The PMDA has recommended that the risk of copper deficiency should be included in product information for polaprezinc, a medicine used to treat gastric ulcer.

Pancytopenia and anaemia have been reported in Japan in poorly nourished patients treated with polaprezinc. These adverse effect may occur because the zinc contained in the medicine inhibits the absorption of copper. Health professionals should monitor their patients and take appropriate measures if any abnormalities are observed.

► *PMDA Summary of investigation results and MHLW Revisions of precautions, 22 November 2016.*

**Brimonidine gel: worsening of rosacea symptoms**

*United Kingdom* – Prescribing advice for brimonidine gel (Mirvaso®) has been updated following an EU-wide review that found worsened rosacea symptoms in up to 16% of patients treated with brimonidine gel in clinical studies. In most cases, the erythema and flushing resolved after the treatment was stopped.

Treatment should be initiated with less than the maximum dose for at least one week, and the dose should be increased gradually based on tolerability and response to treatment. The maximum daily dose (1 g of gel in total weight, approximately 5 pea-sized amounts) should not be exceeded. Patients should be advised to stop treatment and consult a doctor if they notice increased redness or burning during treatment.

► *Drug Safety Update volume 10 issue 4, November 2016: 1.*

**Levonorgestrel emergency contraceptives: interactions with liver enzyme inducers**

*United Kingdom* – The MHRA has informed health professionals that women seeking emergency contraception who have used cytochrome P450 3A4 (CYP3A4) enzyme inducers (such as the antiretrovirals efavirenz and ritonavir, certain medicines for tuberculosis and epilepsy and herbal medicines containing St John’s wort) within the last four weeks should use a copper intrauterine device or, if this is not an option, double the dose of levonorgestrel from 1.5 mg
to 3 mg. Ulipristal acetate emergency contraception is not recommended for use in these women. Advice should also be provided on highly effective ongoing contraception as described in national guidance.

This follows a review of the emergency contraceptive levonorgestrel (Levonelle® and associated names) by the EMA, which found that medicines or herbal remedies that induce CYP3A4 enzymes lower the blood levels of levonorgestrel, which may reduce its emergency contraceptive efficacy.

► MHRA Press release, 15 September 2016.
EMA, Referrals. Levonelle 1500 microgram tablets and associated names.

Direct-acting antivirals: hepatitis B reactivation
United States of America – The FDA has warned health professionals that cases of hepatitis B virus reactivation have occurred in patients co-infected with hepatitis C virus while undergoing treatment with direct-acting antivirals (DAA). Some cases have resulted in fulminant hepatitis, hepatic failure and death.

A "Boxed Warning" is to be added to the product information of daclatasvir (Daklinza®), sofosbuvir and velpatasvir (Epclusa®), ledipasvir and sofosbuvir (Harvoni®), simeprevir (Olysio®), sofosbuvir (Sovaldi®), ombitasvir and paritaprevir and ritonavir (Technivie®), dasabuvir and ombitasvir and paritaprevir and ritonavir (Vieckira Pak®, Vieckira Pak XR®), and elbasvir and grazoprevir (Zepatier®), directing health care professionals to screen and monitor all patients receiving these medicines for hepatitis B virus. (1)

The EMA, Health Canada and the TGA of Australia have performed their own reviews and have issued similar warnings (2, 3, 4). The EMA has confirmed its earlier recommendation to screen all patients for hepatitis B before starting treatment with DAAs, and has concluded that further studies are needed to assess the risk of liver cancer with these medicines.

► (1) FDA Drug safety communication, 4 October 2016.
(2) EMA Press release, 16 December 2016.
(3) Health Canada Advisory, 1 December 2016.
(4) TGA Safety advisory, 19 December 2016.

HIV treatment-boosting agents and steroids: systemic adverse effects
United Kingdom – The MHRA has warned health professionals that the use of steroids metabolized by the cytochrome P450 3A (CYP3A) pathway in patients treated with a HIV treatment-boosting agent may increase the risk of systemic corticosteroid-related adverse effects. Although these reactions are rarely reported, this interaction may occur even with steroid formulations administered by intranasal, inhaled, and intra-articular routes. Coadministration of these medicines is not recommended unless the potential benefit to the patient outweighs the risk. In such cases use of beclomethasone should be considered, particularly for long-term use, as it is less dependent on CYP3A metabolism. Patients should be monitored for systemic corticosteroid-related reactions.

► MHRA. Drug Safety Update vol 10 issue 5, December 2016: 1.
**Nivolumab: immune thrombocytic purpura, myocarditis, rhabdomyolysis**

*Japan* – The PMDA has recommended updates to the product information for the anti-cancer medicine nivolumab (Opdivo®) to warn about the risk of immune thrombocytic purpura, and about the risk of myocarditis and rhabdomyolysis, in addition to myasthenia gravis and myositis that are already mentioned as adverse effects. In the section on precautions, a statement has been added that patients should continue to be monitored after treatment discontinuation as serious adverse effects may still occur at that stage.

The revisions are based on reports of the above-mentioned events in people treated with nivolumab in Japan, and on reported cases of myocarditis and rhabdomyolysis in patients treated with nivolumab in other countries.

► PMDA Summary of investigation results and MHLW Revision of precautions, 18 October 2016.

**Eculizumab: interaction with meningococcal vaccine**

*Canada* – A Health Canada safety review has found that patients with complement-mediated diseases who were treated with eculizumab (Soliris®) had an increased risk of low haemoglobin, including anaemia or haemolysis, after vaccination with Serogroup B meningococcal vaccine (Bexsero®). The risk was highest in patients whose predicted systemic eculizumab concentrations were relatively low.

Health Canada has recommended that patients being treated with eculizumab should be vaccinated only after their disease has been controlled and within one week following eculizumab infusion, when the concentration of eculizumab in the blood is considered to be relatively high. Patients not yet treated with eculizumab should be vaccinated with a meningococcal vaccine (against serotypes A, C, Y, W135, and B) before or at the start of eculizumab treatment, unless the risks of delaying therapy outweigh the risks of developing a meningococcal infection. Patients who started eculizumab treatment less than two weeks after receiving a meningococcal vaccine should receive appropriate prophylactic antibiotics for two weeks after vaccination. The Canadian product information has been updated to include this new safety information.


**Anaesthetics and sedatives in young children and pregnant women**

*United States of America* – Based on a comprehensive analysis of published scientific studies, the FDA has issued a Drug Safety Communication to inform health care providers, parents and caregivers of children younger than three years, and pregnant women in their third trimester, that the repeated or lengthy (more than three hours) use of general anaesthetic and sedation medicines may adversely affect children’s developing brains. The FDA is requiring warnings to be added to the labels of these medicines. The Agency recognizes that in many cases these exposures may be medically necessary and that the potential harms must be carefully weighed against the risk of not performing a specific medical procedure.

► FDA Statement, 14 December 2016.

FDA Drug safety communication, 14 December 2016.
Known risks

**Pioglitazone: bladder cancer**

**United States of America** – The FDA has updated the labelling of products containing the type 2 diabetes medicine pioglitazone to describe the additional studies reviewed on the increased risk of bladder cancer in patients treated with pioglitazone. This follows warnings issued about this risk in 2010 and 2011.

► [FDA Drug safety communication](https://www.fda.gov/Drugs/InformationOnDrugs/ucm502833.htm), 12 December 2016.

**Warfarin and miconazole: contraindicated**

**Japan** – The PMDA, in consultation with the MHLW, has approved an amendment to the product information for miconazole (gel and injection) and for warfarin, to include a contraindication for the two medicines to be used concomitantly due to the increased risk of bleeding.

Health professionals have been advised to prescribe other azole antifungal medicines. The product information for these alternative antifungals has also been updated to advise extreme caution and measures such as more frequent prothrombin time (PT) measurement and thrombotest, due to the increased PT-international normalized ratio (INR) in patients treated with warfarin and other azole antifungals.

These measures follow reports received in Japan of a substantial number of cases of serious bleeding during or after concomitant administration of the two drugs. The revision also took into account reports sent to the MHRA in the United Kingdom about possible interactions of warfarin and miconazole, including haemorrhagic events with fatal outcome. The MHRA is reviewing these data.

The approved product information for topical miconazole in the UK includes a warning that caution should be exercised in patients on oral anticoagulants such as warfarin, and anticoagulant effect should be monitored.

► [PMDA Summary of investigation results](https://www.pmda.go.jp/drug/20161028-1very.html), 18 October 2016.

**Statins: immune-mediated necrotizing myopathy**

**Japan** – The PMDA has recommended updates to the product information for statin-containing products on the market in Japan to warn about the risk of immune-mediated necrotizing myopathy.

In the EU, the approved product information for statins was updated in 2015 to include immune-mediated necrotizing myopathy as an adverse effect occurring with unknown frequency.

► [PMDA Summary of investigation results](https://www.pmda.go.jp/drug/20161028-1very.html), 18 October 2016.

**EMA. PRAC recommendations on signals. Adopted at the PRAC meeting of 6-9 January 2015.**

**Daptomycin: acute generalized exanthemous pustulosis**

**Japan** – The PMDA has recommended to update the product information for the antibacterial medicine daptomycin to warn about the risk of acute generalized exanthemous pustulosis (AGEP). This follows cases of AGEP reported both in Japan and elsewhere.

Approved product information in the EU includes a warning about AGEP, while the U.S. FDA-approved product information mentions that serious skin reactions, including Stevens-Johnson syndrome and...
vesiculobullous rash, have been observed in the post-marketing phase.

► PMDA Summary of investigation results and MHLW Revision of precautions, 18 October 2016.

**NSAIDs: increased risk of miscarriage**

Australia – The TGA has completed a safety review on the known association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the increased risk of miscarriage. The review focused on ensuring that consistent information on this risk was available for all products. The findings confirmed a potential increased risk of miscarriage with non-aspirin NSAIDs, particularly when the medicine is taken close to the time of conception. For aspirin the evidence was not sufficient to confirm an association with the risk of miscarriage.

The TGA is working with sponsors of non-aspirin NSAIDs to harmonize the warnings included in the product information in line with the conclusions of the review.

► TGA Safety advisory, 11 October 2016.

**Paracetamol: updated labelling to address risk of liver injury**

Canada – Health Canada has released an updated labelling standard for over-the-counter paracetamol (U.S. adopted name: acetaminophen), which provides clearer instructions and stronger warnings to help reduce the potential for liver damage. This follows a safety review completed in 2015, which found that more than half of the paracetamol-related cases of serious liver injury reported in Canada were associated with unintentional overdoses.

► Health Canada Information update, 15 September 2016.

**Lurasidone and certain ARVs: contraindicated**

United States of America – The FDA has announced that product information for several antiretrovirals (ARVs) has been updated to add lurasidone (Latuda®), an antipsychotic medicine, to the section on contraindications due to the potential for serious and life-threatening reactions. The ARVs concerned are: tipranavir, indinavir, saquinavir, ritonavir (also in combination with lopinavir), fosamprenavir (if co-administered with ritonavir), darunavir, atazanavir (if co-administered with ritonavir), nelfinavir, and fixed-dose combinations of elvitegravir, cobicistat, emtricitabine and tenofovir. Lurasidone is already included as a contraindicated medication in the product information of atazanavir/cobicistat and darunavir/cobicistat.

In the EU, approved product information for lurasidone includes a contraindication with strong CYP3A4 inhibitors, mentioning some of the above ARVs, and product information for the ARVs warns against co-administration of certain substances that are highly dependent on the CYP3A4 pathway for clearance.

► FDA HIV update bulletin, 19 September 2016.

**Labelling changes**

**Metformin for patients with moderate kidney impairment**

European Union – The EMA has completed a review of the antidiabetic metformin and has concluded that the
medicines can be given to patients with type 2 diabetes that have moderately reduced kidney function (glomerular filtration rate of 30–59 ml/min). Reduced doses should be considered for these patients according to the dosage recommendations to be provided in the updated product information. The contraindication for patients with severely reduced kidney function (glomerular filtration rate less than 30 ml/min) will remain.

Previously, metformin had not been recommended in patients with impaired kidney function because of the risk of lactic acidosis. The review found that the large patient population with moderately reduced kidney function can benefit from the use of metformin. Product information for metformin-containing medicines approved in the EU is being revised and harmonized to reflect current scientific evidence and recommendations.

► EMA Press release, 14 October 2016.

**Etoricoxib: lower recommended dose**

**United Kingdom** – The marketing authorization holder, in communication with MHRA, has informed health professionals of a revised dosing recommendation for etoricoxib (Arcoxia®) when used to treat rheumatoid arthritis or ankylosing spondylitis. The recommended starting dose has been lowered to 60 mg daily, with the option to increase to a maximum of 90 mg once daily if necessary. Once the patient is clinically stabilised, down-titration to 60 mg once daily may be appropriate. In the absence of therapeutic benefit, other treatment options should be considered.

The cardiovascular risk, and other important risks of etoricoxib, may increase with dose and duration of exposure. Therefore the lowest effective daily dose should be used and the need for treatment should be regularly reassessed. The recommendation is based on results of two clinical trials showing that the 60 mg-dose is effective in some but not all patients.


**Improved dosing instructions**

**Levetiracetam oral solution**

**European Union** – Cases of accidental overdoses with levetiracetam oral solution (Keppra®) have been reported in Europe, with the majority of cases occurring in children aged between 6 months and 11 years. Where the cause of the reported overdosing could be determined, it was either due to the use of an inappropriate syringe or the misunderstanding of the caregiver about how to measure the dose.

The EMA has recommended new measures to ensure the safe use of levetiracetam oral solution. Different colours will be used for the outer packaging and bottle labels of the different presentations. Prescribers should ensure that they prescribe the age-appropriate presentation of the medicine, indicating the dose in mg with a ml equivalence based on the correct age of the patient. Pharmacists should ensure that the appropriate presentation is dispensed. With every prescription, healthcare professionals should advise the patient and/or caregiver on how to measure the prescribed dose, reminding them to use only the syringe included in the package with each bottle and to discard the syringe once the bottle is empty.

► EMA Press release, 14 October 2016.
Unchanged recommendations

Urine- and plasma-derived medicines: safe regarding Zika

European Union – The EMA has confirmed that there is no increased risk of contamination with the Zika virus for patients who take plasma-derived medicines such as coagulation factors or immunoglobulins, or urine-derived medicines such as certain hormone-based treatments or urokinase products.

A review of information showed that the manufacturing processes used for plasma-derived products, such as the solvent/detergent method to inactivate viruses, liquid heat inactivation and virus filtration, inactivate or remove the Zika virus from the finished product. Likewise, manufacturing processes for urine-derived products contain complementary steps with inactivation/removal capacity for enveloped viruses, which are considered sufficient to ensure the Zika virus safety of these products. The EMA concluded that no additional safety measures such as screening, testing, deferral or exclusion of certain donors are necessary.


15 September 2016.

Non-compliance with good practices

Pharmaceutics International Inc., U.S.: import stop to EU

European Union – The EMA has recommended that medicines manufactured by Pharmaceutics International Inc., United States, should no longer be supplied in the EU. The only exception is sodium phenylbutyrate (Ammonaps®), a medicine used to treat urea cycle disorders which is considered to be critical for public health. In countries where alternatives are available Ammonaps® will be recalled. Certain other medicines supplied by Pharmaceutics International Inc. are available from alternative registered manufacturing sites and will remain available in the EU.

These precautionary measures follow a review that was triggered by inspection findings of continued non-compliance with good manufacturing practice.

► EMA Press release, 16 September 2016.

Safety reviews started

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<th>Under review</th>
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<td>Medicine: Certain injectable methyl-prednisolone products used to treat severe, rapidly developing (acute) allergic reactions</td>
<td>Traces of cows’ milk proteins could affect treatment of acute reactions in the small number of highly sensitive patients allergic to lactose. The reaction to the medicine may be mistaken for a worsening of the original condition, leading to additional doses of the medicine being given.</td>
<td>► EMA. Article 31 Referral started. EMEA/ H/A-31/1449. 1 December 2016.</td>
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| Contract research organization: Micro Therapeutic Research Labs, India | Inspection findings of non-compliance with good clinical practice at the study sites in Chennai and Coimbatore, India |► EMA. Article 31 Referral started. 16 December 2016. |