Safety news

Safety warnings

Azithromycin: Long term risks seen in clinical study
Ireland, Estonia – The marketing authorization holder, in agreement with EMA and national regulatory authorities, has informed health professionals about an increased rate of relapses of haematological malignancies and mortality in haematopoietic stem cell transplantation (HSCT) patients treated experimentally with azithromycin. A clinical trial investigating the use of azithromycin to prevent bronchiolitis obliterans syndrome following HSCT was terminated early after an increased risk of relapses was seen compared with placebo. The researchers conclude that long term azithromycin exposure following HSCT may include risks which exceed the anticipated benefits.
► HPRA Safety notice, 2 May 2018.
Ravimiamet Safety announcement, 2 May 2018 (in Estonian).

Tosufloxacin: Nephrogenic diabetes insipidus
Japan – The PMDA has informed health professionals that cases of nephrogenic diabetes insipidus have been observed with the fluoroquinolone antimicrobial tosufloxacin in Japan. A warning about this adverse effect will be added to the product information.
► PMDA Summary of investigation results and MHLW Revision of precautions, 19 April 2018.

Dolutegravir: Birth defects
A study involving babies born to 11 558 HIV-positive women in Botswana— the Tsepamo Study— showed that 0.9% of babies (4 of 426) whose mothers became pregnant while taking dolutegravir had a neural tube defect, compared with 0.1% of babies (14 of 11 173) whose mothers took other HIV medicines.

European Union, Australia, United States of America – Regulatory authorities around the world have issued precautionary advice in response to the study findings. The EMA and the TGA have recommended that dolutegravir should not be prescribed to women seeking to become pregnant. Women who can become pregnant should use effective contraception while taking dolutegravir medicines. (1,2) The FDA has recommended that health professionals should exclude pregnancy before starting a dolutegravir-containing regimen in women of childbearing age, and should only prescribe the medicine to women of childbearing age if they decide that its benefits outweigh the risks. In that case, they should reinforce the need for effective contraception. (3) The regulatory authorities will continue to investigate the issue.
► (1) EMA Press release, 18 May 2018.
(2) TGA Safety advisory, 31 May 2018.
(3) FDA Drug safety communication, 18 May 2018.

Geneva – WHO has convened an expert guideline development group meeting and will release updated guidance on the role
of dolutegravir in first- and second-line HIV treatment in the coming months. In the interim, WHO advises countries and ministries to follow the 2016 WHO ARV Guidelines, and to consider the following:

- Pregnant women who are taking dolutegravir should not stop their ARV therapy and should speak with their health provider for additional guidance.
- Antiretroviral (ARV) therapy for women of childbearing age, including pregnant women, should be based on drugs for which adequate efficacy and safety data are available; an efavirenz–based regimen is a safe and effective first-line regimen.
- If other first-line ARVs cannot be used in women of childbearing age, dolutegravir may be considered in cases where consistent contraception can be assured.
- Programmes should continue strengthening pharmacovigilance including monitoring of birth outcomes. The WHO Guidelines released in 2016 cautioned that there were insufficient data for using dolutegravir during pregnancy or breastfeeding and recommended efavirenz, in combination with tenofovir and lamivudine or emtricitabine, as the preferred option in pregnancy.

If a leakage occurs during the reconstitution of lyophilized vaccines, the syringe should be discarded. If leakage is observed during the administration of a vaccine, the doctor must decide whether the individual concerned should be revaccinated. The potential benefit of increasing vaccination protection should be weighed against the risk of adverse events due to administration of a second full dose.

Details of the vaccines affected and further information are found in the regulatory communications referenced below.

- Swissmedic Healthcare professional communication, 13 April 2018 and company information letter
- Health Canada Advisory, 1 May 2018.

Pembrolizumab, atezolizumab:

- Use restricted in EU
- Reports of sclerosing cholangitis with pembrolizumab in Japan

European Union – The EMA has restricted the use of pembrolizumab (Keytruda®) and atezolizumab (Tecentriq®) in first-line treatments for urothelial cancer. For this indication the medicines should now only be used in patients with high levels of PD-L1 protein. Early data from two clinical trials have shown reduced survival in patients with low PD-L1 levels. There is no change in the recommended use of the two medicines for second-line treatment, or for treatment of other cancers.\(^{(1)}\)

Japan – The PMDA has informed health professionals about cases of sclerosing cholangitis reported in patients treated with pembrolizumab in Japan. Sclerosing cholangitis is characterized by swelling due to inflammation, scarring and destruction of
the bile ducts inside and outside of the liver. The product information will be updated to warn about this risk.

► (1) EMA Press release, 1 June 2018.
► (2) PMDA Summary of investigation results and MHLW Revisions of precautions, 19 April 2018.

Filgrastim and other G-CSFs: Aortitis
Ireland – The marketing authorization holders, in agreement with HPRA, have informed healthcare professionals that there have been rare reports of aortitis in patients and healthy donors receiving products containing the granulocyte colony-stimulating factors (G-CSFs) filgrastim, lenograstim, lipegfilgrastim or pegfilgrastim. People receiving a G-CSF product should be instructed to seek medical attention if they develop fever, abdominal pain, malaise or back pain. (1)

The EMA’s PRAC had evaluated this safety signal in February 2018 and had recommended that the product information of the G-CSF products on the European market should be updated to reflect the risk of aortitis. (2)

► (1) HPRA Safety notice, 17 May 2018.
► (2) EMA. PRAC recommendations on signals. Adopted at the 5-8 February 2018 PRAC meeting. 22 February 2018.

Denosumab (indicated in fractures, bone neoplasm metastasis): new malignancies
Ireland, Estonia – The marketing authorization holder, in agreement with EMA and the national regulatory agencies, has informed health professionals of new study findings concerning denosumab (Xgeva*). New primary malignancies were reported more frequently in clinical studies in patients with advanced malignancies treated with denosumab, compared to zoledronic acid (cumulative incidence at one year: 1.1% versus 0.6%). No treatment-related pattern in individual cancers or cancer groupings was apparent. The product information will be updated to include this information.

► HPRA Safety notice, 17 May 2018.

Lamotrigine: Rare but serious immune reaction
United States of America – The FDA has warned that lamotrigine (Lamictal*) can cause haemophagocytic lymphohistiocytosis (HLH), a rare but very serious immune system reaction. HLH causes an uncontrolled response by the immune system and typically presents as a persistent fever. It can lead to severe problems with blood cells and organs such as the liver, kidneys, and lungs and can be fatal, especially if it is not diagnosed and treated quickly.

Lamotrigine is used to treat seizures and bipolar disorder. A new warning about this risk has been added to the product information for lamotrigine-containing medicines.

► FDA Drug safety communication, 25 April 2018.

Veterinary ear gel: Eye injuries in pets and owners
European Union – The EMA has warned that an ear gel for dogs containing terbinafine, florfenicol and betamethasone acetate (Osurnia*) has been causing eye injuries to pets or their owners after
accidental eye exposure. Care should be taken to prevent the ear gel from getting into the eyes of people or dogs. If accidental exposure occurs, the eyes should be thoroughly rinsed with water, and medical care sought. Veterinary healthcare professionals in the EU will be informed in writing of this issue.

► EMA Press release, 20 April 2018.

**Known risks**

**Anagliptin, linagliptin, teneligliptin:**

**Acute pancreatitis**

Japan – The MHLW has recommended updates to the product information for the antidiabetic medicines anagliptin, linagliptin and teneligliptin following cases of acute pancreatitis reported in patients treated with these medicines in Japan.

A warning about post-marketing reports of acute and potentially fatal pancreatitis is also found in the EMA- and FDA-approved product information for products containing linagliptin and other dipeptidyl peptidase-4 (DPP-4) inhibitors.

► PMDA Summary of investigation results and MHLW Revisions of precautions, 20 March 2018.

**Selexipag:**

**Avoid use with CYP2C8 inhibitors**

Japan – Based on the results of a drug-drug interaction study involving selexipag (Uptravi®) and gemfibrozil, a strong CYP2C8 inhibitor, the PMDA has recommended that selexipag should be contraindicated in Japan in patients receiving medicines containing clopidogrel, which is also a CYP2C8 inhibitor. Selexipag is used to treat pulmonary hypertension.

Gemfibrozil is not currently approved in Japan.

In the EU and the U.S. selexipag is contraindicated with gemfibrozil but can be used with moderate CYP2C8 inhibitors (such as clopidogrel, deferasirox or teriflunomide), although dose adjustments should be considered.

► PMDA Summary of investigation results and MHLW Revisions of precautions, 20 March 2018.

**Tolvaptan:**

**Acute liver failure**

Japan – The PMDA has informed health professionals that cases of acute liver failure, including several fatal cases, have been reported in patients treated with tolvaptan in Japan. This medicine is used to treat hyponatraemia and – at higher doses – to slow the progression of autosomal dominant polycystic kidney disease, a rare inherited condition. The currently approved product information recommends close monitoring of liver function. The MHLW has requested that a warning about the risk of acute liver failure should be added.

Warnings about serious and potentially life-threatening liver injury are also included in the EMA- and FDA-approved product information.

► PMDA Summary of investigation results and MHLW Revisions of precautions, 20 March 2018.

**Oral benzocaine products:**

**Rare but serious blood disorder**

United States of America – In an update to two previous communications the FDA has warned about the risk of methaemoglobinæmia associated with oral benzocaine-containing products. This is
a serious and potentially life-threatening blood disorder in which the amount of oxygen carried through the blood is greatly reduced.

The FDA has urged manufacturers to stop marketing over-the-counter oral benzocaine products for teething and mouth pain in children under two, and to include certain warnings in the product information of oral benzocaine products for adults and children aged two years and above. The FDA will take action if companies do not comply.

► FDA Drug safety communication, 23 May 2018.

Updated recommendations

Ulipristal

European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of ulipristal acetate (Esmya*), leading to new measures to minimize the risk of rare but serious liver injury. Ulipristal is now contraindicated in women with known liver problems. New treatment courses may be started only if patients are tested and have liver enzyme levels at most 2 times the upper limit of normal. Tests should be repeated once a month during the first two treatment courses and two to four weeks after stopping treatment. If liver enzyme levels rise above 3 times the upper limit of normal, treatment should be stopped and the patient closely monitored. Ulipristal should be used for more than one treatment course only in women who are not eligible for surgery. A card will be included with the medicine to inform women about the need for liver monitoring and for seeking medical help in case of suspected liver problems.

Ulipristal is used to treat moderate to severe symptoms of uterine fibroids. The review was triggered in November 2017 by reports of serious liver injury. In February 2018 the PRAC had issued interim recommendations against starting ulipristal in new patients.

► EMA Press release, 1 June 2018.

Antimicrobials

Japan aligns product information

Japan – The PMDA has recommended that the product information for 164 antimicrobial medicines approved in Japan be updated in line with the national Guidance for Appropriate Use of Antimicrobials. This guidance focuses on the appropriate treatment of patients with acute respiratory tract infections and those with acute diarrhoea. Based on data from Japan and other countries, these two patient groups are believed to be subjected to particularly frequent and unnecessary antimicrobial treatment. The affected medicines are indicated for the treatment of pharyngitis/laryngitis, tonsillitis, acute bronchitis, infectious enteritis or sinusitis.\(^{(1)}\)

In other moves to align the product information in Japan with that approved elsewhere, the Agency has recommended that adrenaline can be used for emergency treatment of anaphylaxis in patients receiving alpha blockers, despite the risk of decreased blood pressure induced by adrenaline reversal,\(^{(2)}\) and propofol can be given to pregnant women, or women who may be pregnant, provided that the potential
benefits outweigh the risk of neonatal respiratory depression. (3)

(2) PMDA Report on investigation results, 2 March 2018.

Dengue vaccine
Geneva – WHO’s Strategic Advisory Group of Experts on Immunization (SAGE) has published its revised recommendations on the use of the dengue vaccine CYD-TDV (Dengvaxia®). Results from additional safety studies conducted by the manufacturer had shown that the vaccine is associated with an increased risk of severe dengue in seronegative individuals, starting about 30 months after the first dose.

The SAGE weighed two strategies for achieving high population protection from dengue: consideration of population seroprevalence criteria, and pre-vaccination screening. Acknowledging that both are programmatically difficult, the SAGE expressed its preference for screening and vaccinating only dengue-seropositive persons.

Screening can be done using the dengue IgG ELISA, interpreted in a local context depending on the prevalence of other flaviviruses and past use of flavivirus vaccines (such as Japanese encephalitis and yellow fever vaccines), or—in high transmission settings—rapid tests, although these have a lower sensitivity and specificity than serological testing. Decisions about implementing pre-vaccination screening will require careful assessment of the sensitivity and specificity of available tests, local priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both CYD-TDV and screening tests in each country.

Going forward there is a need to develop a highly sensitive and specific rapid diagnostic test, and to simplify immunization schedules.

► WHO. Revised SAGE recommendation on use of dengue vaccine. 19 April 2018.

Daclizumab: Risk outweigh benefits
European Union – The EMA has confirmed that the multiple sclerosis medicine daclizumab beta (Zinbryta®) poses a risk of serious and potentially fatal immune reactions affecting the brain, liver and other organs. The marketing authorization in the EU was voluntarily withdrawn by the company in March 2018. Healthcare professionals should continue monitoring patients who have been treated with daclizumab in line with recommendations issued in March 2018. (1)

Australia – The TGA has informed health professionals that the marketing authorization holder is coordinating a worldwide withdrawal of daclizumab. To give time for patients to transition off the medicine it will be supplied in Australia until 31 May 2018. (1)

(2) TGA Alert, 15 March 2018.
Other updates

**Hydroxyethyl starch:**
*Suspension maintained*

European Union – Following the recommendation by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) in January 2018 to suspend the marketing authorizations for hydroxyethyl starch solutions for infusion across the EU, the European Commission had requested the Committee to further consider any possible unmet medical need that could result from the suspension, as well as the feasibility and likely effectiveness of additional risk minimization measures.\(^{(1)}\) At its meeting held in May 2018 the PRAC maintained its recommendation. In line with regulatory procedure this recommendation was then sent to the Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh) of the European Heads of Medicines Agencies (HMA) network for its consideration.\(^{(2)}\)

\(^{(1)}\) EMA News, 13 April 2018.
\(^{(2)}\) EMA News, 18 May 2018.

**Quinolones and fluoroquinolones:**
*Public hearing*

European Union – Quinolone and fluoroquinolone antibiotics are under review by the PRAC due to the risk of persistent serious side effects mainly affecting muscles, joints and the nervous system. In response to significant public interest, a public hearing was scheduled for 13 June 2018.\(^{(1)}\) The EMA received 115 applications to attend, including 55 requests to speak and 60 to participate as observers. Of the former, 23 speakers from 11 EU Member States were selected to share their views directly with the PRAC; the other 22 will provide written contributions that will be considered by the scientific committee and published on the EMA website.\(^{(2)}\)

This is the second public hearing during an EMA safety review of a medicine. The first one was held in September 2017 to inform the review of valproate, leading to additional measures to avoid its use in pregnancy.

\(^{(1)}\) EMA Press release, 9 April 2018.
\(^{(2)}\) EMA Press release, 7 June 2018.
## Reviews started

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Use</th>
<th>Concerns</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Omega-3 fatty acid medicines</strong></td>
<td>Prevention of recurring heart disease or stroke</td>
<td>An analysis of 10 studies in around 78 000 patients has found that adding omega 3-fatty acid medicines to standard treatment did not significantly reduce heart attacks, stroke or other heart and circulatory problems. These findings were similar to those from 2012 studies.</td>
<td>EMA, Start of Article 31 referral. 22 March 2018.</td>
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<tr>
<td><strong>Ulipristal acetate</strong> (Fibristal®)</td>
<td>Treatment of uterine fibroids</td>
<td>Canadian and European reports of serious adverse events affecting the liver. The EMA has recommended new measures to minimize the risk (see page 203).</td>
<td>Health Canada Advisory. 15 March 2018.</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>Treatment of inflammatory diseases, such as arthritis and psoriasis; treatment of certain cancers</td>
<td>Dosing errors, causing continued reports of serious adverse events, including fatalities. Methotrexate is used in higher doses and frequency to treat cancer than to treat inflammatory diseases.</td>
<td>EMA Press release, 13 April 2018.</td>
</tr>
<tr>
<td><strong>Metamizole</strong> (also known as dipyrrone)</td>
<td>Treatment of severe pain and fever that cannot be controlled with other treatments</td>
<td>Substantial differences between EU member states in recommended maximum daily doses and contraindications during pregnancy or in women who are breastfeeding.</td>
<td>EMA begins review of medicines containing metamizole. 1 June 2018.</td>
</tr>
<tr>
<td><strong>Curcumin-containing supplements</strong></td>
<td>Dietary supplements for joint, digestive and cardiovascular support</td>
<td>Potential interaction with warfarin that could lead to an increased risk of bleeding. A marked INR increase was reported in a patient on warfarin in New Zealand after starting curcumin supplements.</td>
<td>Medsafe Monitoring communication. 17 April 2018.</td>
</tr>
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</table>
Falsified medicines

Falsified hepatitis B vaccines circulating in Uganda

The **WHO Medical Product Alert No. 3/2018** relates to falsified versions of multi-dose (10ml) hepatitis B vaccines (rDNA) that have been identified in Uganda.

WHO was informed by the Uganda National Drug Authority (NDA) that this falsified vaccine was available at patient level in a number of locations in the Central, South-Western and Eastern regions of Uganda. Investigations are ongoing, and samples are being collected for full laboratory analysis. The source of the falsified product has not yet been identified.

The genuine product is manufactured by the Serum Institute of India Pvt Ltd and is WHO-prequalified. Falsified versions of 10 different batch numbers have so far been discovered (see below). Based on label inconsistencies the Serum Institute of India has confirmed that the products with these details are falsified.

No adverse reactions have been reported to WHO at this stage.

<table>
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<tr>
<th>Product name: Multi dose (10ml) Hepatitis B Vaccines (rDNA)</th>
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<tr>
<td>False manufacturer name stated on the label: Serum Institute of India</td>
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<table>
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<tr>
<th>Batch number</th>
<th>Manufacturing date</th>
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<td>035L006</td>
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<tr>
<td>035L5007</td>
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<td>07/2018</td>
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</tbody>
</table>


PDF version (includes photographs)

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