Safety news

Restrictions

**Nicorandil: Use only as second-line angina treatment**

United Kingdom – The MHRA has advised health professionals that nicorandil should only be used as second-line treatment for stable angina when patients do not sufficiently respond to, do not tolerate or should not take medicines such as beta-blockers and/or calcium antagonists. Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula, or abscess. Treatment with nicorandil should be stopped if ulceration occurs, and alternative treatment or specialist advice considered if angina symptoms worsen. (1)

This advice reflects harmonized product information, labelling and package leaflets for nicorandil (Ikorel®, Dancor® and associated names) across the European Union as recommended by EMA in March 2015. The harmonized product information also includes updated advice on the medicine’s posology, contraindications and precautions for use. (2)

(2) EMA. Questions and answers on Ikorel, Dancor and associated names (nicorandil, 10 and 20 mg tablets). 5 June 2015.

**Fosamprenavir: contraindicated with paritaprevir**

European Union – A new contraindication has been added to the approved product information of the antiretroviral medicine fosamprenavir (Telzir®). The medicine should not be co-administered with paritaprevir due to the expected increase of paritaprevir exposure and the lack of clinical data assessing the magnitude of this increase.


**Ombitasvir / paritaprevir / ritonavir: extended contraindication**

Japan – The PMDA has extended the contraindication for the antiviral combination ombitasvir hydrate/paritaprevir hydrate/ritonavir (Viekierax®) to include patients with moderate liver impairment (patients Child-Pugh Class B) in addition to those with severe liver impairment (Child-Pugh Class C). A warning has been added to the product information that blood bilirubin level may significantly increase, and hepatic failure may be observed along with ascites, hepatic encephalopathy and other effects. Patients should be carefully monitored. If any signs of liver failure are observed the drug should be discontinued and appropriate measures adopted.


**Erlotinib: only for certain types of non-small cell lung cancer**

European Union, New Zealand – Results of a recent study have indicated that erlotinib (Tarceva®) is only of benefit
in the first line maintenance treatment of non-small cell lung cancer in patients whose tumours harbour an EGFR-activating mutation. Product information updates have been recommended accordingly by a number of regulatory authorities (1, 2, 3).

(2) EMA Summary of opinion (post authorization), 17 December 2015.

Safety warnings

Thalidomide: reduced starting dose in patients over 75 years
United Kingdom – In line with EMA recommendations, the MHRA and the marketing authorization holder have informed health professionals that the starting dose of thalidomide has been reduced to 100 mg/day in patients over 75 years, to minimize the risk of adverse drug reactions.

Thalidomide combined with melphalan and prednisone is indicated as first-line treatment of certain patients with untreated multiple myeloma. The starting dose of melphalan in patients over 75 years of age should be 0.1–0.2 mg/kg daily, according to baseline bone-marrow reserve and renal function. Prescribers should be aware that even with a reduced starting dose of thalidomide, this age group may be at higher risk of serious adverse reactions than younger patients.

► Drug Safety Update volume 9 issue 5, December 2015: 1.

Nintedanib: avoid in hepatic function disorder
Japan – The PMDA has recommended that the use of nintedanib (Ofev®) should be avoided in patients with moderate to severe hepatic function disorder (Child-Pugh B and C) unless treatment with this drug is deemed necessary. The results from the clinical pharmacokinetic study, which was ongoing at the time of approval, showed that blood concentration of nintedanib ethanesulphonate increased in patients with hepatic function disorder.

Nintedanib is used to treat idiopathic pulmonary fibrosis. Approved product information in the United States and the EU states that the medicine is not recommended for use in patients with moderate to severe liver problems as it has not been studied in these patients.


Lenvatinib: tumour haemorrhage
Japan – The PMDA has warned that lenvatinib (Lenvima®), approved for the treatment of unresectable thyroid cancer, may cause carotid arteries haemorrhage or tumour haemorrhage associated with tumour shrinkage or necrosis. Furthermore, there have been case reports of development of massive bleeding from exposed carotid artery sites or fistula formulation sites. There is a risk of haemoptysis or haematemesis in patients with a tracheal fistula or oesophageal fistula.

The medicine should be used with caution in patients with tumour invasion in the carotid arteries, veins or other sites; this is seen in many patients with anaplastic thyroid cancer. Patients should be carefully monitored during
administration of the drug, and the presence or absence of fistula formation should be confirmed. In case of haemorrhages, administration of lenvatinib should be discontinued as necessary and appropriate measures taken.


**Biphosphonates: very rare osteonecrosis of external ear canal**

**United Kingdom** – The MHRA has advised health professionals to consider the possibility of osteonecrosis of the external auditory canal in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, and in patients with suspected cholesteatoma. Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. Patients should be advised to report any ear pain, discharge from the ear or an ear infection during bisphosphonate treatment.

Evidence from the clinical literature and from reported cases supports a causal association between bisphosphonates and osteonecrosis of the external auditory canal. Product information for bisphosphonates available in the United Kingdom (alendronic acid, ibandronic acid, pamidronate disodium, risedronate sodium, sodium clodronate and zoledronic acid) has been updated.


**Atovaquone: agranulocytosis and leukopenia**

**Japan** – Following 11 reported cases of agranulocytosis and leukopenia in patients treated with atovaquone, including two fatal cases and five others for which causality could not be ruled out, the PMDA has recommended that product information for atovaquone-containing products (Samitrel®, Malarone®) should be updated to include this risk. Patients should be carefully monitored. If any abnormalities are observed, atovaquone should be discontinued and appropriate measures adopted.


MHLW Revisions of precautions and PMDA Summary of investigation results. 12 January 2016.

**Known risks**

**SGLT-2 inhibitors: ketoacidosis and urinary tract infections**

**United States of America** – Following its drug safety communication of 5 May 2015, the FDA has added warnings to the product information for the sodium-glucose cotransporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin. These antidiabetics can cause ketoacidosis and serious urinary tract infections. Ketoacidosis can occur even if the blood sugar level is not very high. If ketoacidosis is suspected, the SGLT2 inhibitor should be discontinued and treatment instituted promptly. (1)

**European Union** – The EMA has made recommendations to minimize the risk of diabetic ketoacidosis associated with SGLT2 inhibitors, including in atypical cases where blood sugar levels are not as high as expected.

Patients should be made aware of risk factors and symptoms of ketoacidosis and should be asked to contact their health
care professional if they have any of these symptoms.

If diabetic ketoacidosis is suspected or confirmed, treatment should be stopped immediately and should only be re-started if another cause for the ketoacidosis is identified and resolved. Caution should be exercised in patients with risk factors for ketoacidosis, which include a low reserve of insulin-secreting cells, conditions that restrict food intake or can lead to severe dehydration, a sudden reduction in insulin or an increased requirement for insulin due to illness, surgery or alcohol abuse. In patients hospitalized for major surgery or serious illness SGLT2-inhibitor treatment should be stopped temporarily.

Health professionals have been reminded that these medicines are only authorized for treating type 2 diabetes, not type 1 diabetes.

► (1) FDA Drug Safety communication, 4 December 2015.
► (2) EMA Press release, 26 February 2016.

See also: Medsafe Prescriber Update 36(4): 57-58, December 2015

Elvitegravir/cobicistat/emtricitabine/tenofovir: interactions with anticonvulsants

Japan – The PMDA has recommended that the antiviral combination elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild®) should not be administered concomitantly with anticonvulsants such as carbamazepine, phenobarbital, phenytoin or fosphenytoin. Approved product information in the EU includes a contraindication in patients treated with these anticonvulsants.


Nivolumab: diabetes mellitus and ketoacidosis

Japan – The PMDA has recommended updates to the product information of cancer medicine nivolumab (Opdivo®) to warn about the risk of type 1 diabetes mellitus – including the fulminant type – and diabetic ketoacidosis. Patients should be monitored for symptoms such as thirst, nausea and vomiting or increase in blood glucose levels. If type 1 diabetes mellitus is suspected, nivolumab should be stopped and appropriate measures taken, such as administration of insulin.

Product information in the EU mentions diabetes mellitus and ketoacidosis as uncommon adverse effects.


Natalizumab: new measures to manage PML

European Union – The EMA has recommended new measures to minimize the risk of progressive multifocal leukoencephalopathy (PML) with the multiple sclerosis medicine natalizumab (Tysabri®). PML is a rare and very serious brain infection caused by John Cunningham (JC) virus.

Patients considered as being at high risk for PML are those who were treated with immunosuppressants before starting natalizumab and have antibodies against JC virus and have been on natalizumab for more than two years. For these patients more frequent MRI scans (e.g. every 3-6 months) should be considered to enable detection and early treatment of asymptomatic cases, thus limiting the degree of potential brain damage. In these patients, treatment with natalizumab...
should only be continued if benefits outweigh the risks. In patients who have not been treated with immunosuppressants before starting natalizumab, the level of antibodies (index) relates to the level of risk for PML. The antibody test should be repeated every 6 months in patients who tested negative, as well as those with antibody index values of 0.9 or less once they have been on natalizumab for longer than two years. Patients with index values above 1.5 and on treatment for longer than two years are considered to be at higher risk for PML and should be managed as described above.

If PML is suspected at any time, treatment with natalizumab must be stopped until PML has been excluded. ► EMA Press release, 26 February 2016.

Fingolimod: new measures to minimize PML and BCC risks

European Union – The European Medicines Agency (EMA) has recommended new monitoring measures to minimize the risks of progressive multifocal leukoencephalopathy (PML) and basal cell carcinoma related to the immunosuppressive effect of the multiple sclerosis medicine fingolimod (Gilenya®).

PML has been reported in patients treated with fingolimod, including in some not previously treated with another immunosuppressive medicine. A baseline MRI scan should be available usually within three months of starting treatment. If PML is suspected, MRI should be performed immediately and fingolimod should be stopped until PML has been excluded. If an anti-JC virus antibody test is done, it should be considered that the the presence of lymphopenia may possibly affect the outcome, and that JC virus infection may still occur after a negative test.

With regard to the risk of basal cell carcinoma, a medical evaluation of the skin is recommended before starting treatment with fingolimod, after at least one year and then at least yearly. Fingolimod must not be used in patients with basal cell carcinoma or any other type of cancer. Patients should be instructed to look for signs of basal cell carcinoma and seek medical advice if they occur. Patients should be referred to a dermatologist if they have lesions suggestive of BCC. ► (1) EMA Press release, 18 December 2015.

Methylphenidate: hepatic failure

Japan – Following reports of hepatic failure and hepatic function disorder in patients treated with methylphenidate tablets (Concerta®, Ritalin®) outside Japan, the PMDA has reviewed available data, and the Ministry of Health, Labour and Welfare (MHLW) has recommended revisions to the package insert.

Product information approved in the UK lists hepatic enzyme elevations as rare, and abnormal liver function including hepatic coma as very rare adverse effects. ► MHLW Revisions of precautions and PMDA Summary of investigation results, 16 February 2016.

Varenicline: psychiatric symptoms and potential alcohol interaction

Australia – The TGA has recommended updates to the product information for the smoking cessation medicine varenicline (Champix®) to strengthen the warnings about the risk of psychiatric symptoms which may include depression, anxiety, agitation, aggression, mood swings, self-harm, thoughts of self-harm, or seeing,
hearing or sensing things that are not there. Alcohol consumption may increase these risks. Patients experiencing such symptoms should stop taking varenicline and contact a health professional immediately. The TGA will continue to monitor the issue.
► TGA Safety advisory, 2 December 2015.

Label changes

Posaconazole: dosing of oral formulations not interchangeable
United States of America – The FDA has approved labelling changes to help prevent dosing errors when switching between the oral suspension and delayed release tablet formulations of the antifungal medicine posaconazole (Noxafil®). Wording has been added to indicate that these two formulations cannot be directly substituted for each other but require a change in dose.
Since November 2013, the FDA has received eleven reports of the wrong oral formulations being prescribed and/or dispensed to patients. One case resulted in death, another in hospitalization.

FDA restrictions for rosiglitazone had been removed in 2013 since data did not demonstrate an increased risk of heart attack compared to metformin and sulfonylurea. The training requirements have been fulfilled, and no new pertinent safety information has been identified.
► FDA Drug safety communication, 16 December 2015.

Unchanged recommendations

Rivaroxaban: clinical trial conclusions maintained
European Union – The European Medicines Agency (EMA) has concluded that the benefit-risk balance of rivaroxaban in patients with non-valvular atrial fibrillation remains unchanged, despite a defect with the international normalised ratio (INR) device used in the main clinical study supporting its use.
The study compared rivaroxaban with warfarin. There were concerns that the defective INR device could have provided lower INR values in some patients in the warfarin group, potentially leading to dose increases and therefore a higher risk of bleeding. After further data analyses the EMA’s Committee for Medicinal Products for Human Use (CHMP) concluded that the defective device would have had only a marginal effect on the study results and the conclusions would not be affected.
Data from other large studies confirmed the comparative safety of rivaroxaban and showed similar rates of bleeding in their warfarin groups.
### Medicines quality

**Pharmaceuticals from Tianjin City region: potential contamination**

*United States of America* – The FDA has alerted drug compounders and manufacturers that drug shipments from Tianjin, China are at risk of chemical contamination as a result of two massive explosions at a chemical warehouse of Tianjin Dongjiang Port Ruihai International Logistics Co. in August 2015. More than 40 different types of chemicals were discovered at the blast site.

Increased FDA surveillance resulted in the detection of hydrogen cyanide contamination in two shipments of drugs from Tianjin Tianyao Pharmaceuticals Co. Ltd located approximately 30 kilometres from the explosion site. The shipments were stopped, and the FDA is working with the Chinese Food and Drug Administration (CFDA) on the issue. Hydrogen cyanide was not detected in two other drug shipments sent to the United States by the same company since the explosion.

The FDA has reminded pharmaceutical companies that it is their responsibility to know the source of the ingredients and finished products that they obtain, and to

### Safety reviews

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take appropriate precautions to ensure their quality.

► CDER Alert, 22 December 2015.

**Baclofen active pharmaceutical ingredient: potential contamination**

**United States of America** – The FDA has warned that baclofen active pharmaceutical ingredient (API) from Taizhou Xinyou Pharmaceutical & Chemical Co. Ltd, China, may be at risk for contamination with particulates and should not be used to manufacture or compound sterile injectable drugs.

The FDA has informed compounders in the United States that injectable products compounded with the affected API could pose serious safety risks, especially when administered directly into the spinal column. They may also clog pumps used to administer the medication. There is a potential risk that the baclofen API may be contaminated by endotoxin or microorganisms. The FDA is continuing to investigate this incident. (1)

**Australia** – The TGA has determined that none of the products included on the Australian Register of Therapeutic Goods contain the baclofen API manufactured by Taizhou Xinyou Pharmaceutical & Chemical Co. Ltd. However, it has been used by some Australian compounders. The TGA has advised that this API should not be used to compound sterile injectable medicines. (2)

► (1) FDA Statement, 9 December 2015.

(2) TGA Medicines Safety Update Volume 7 Number 1, February 2016.

**Notice of concern for Cadila Healthcare Ltd**

**Geneva** – The WHO prequalification team has informed the public that issues considered of concern have been noted in a GMP inspection conducted on 26–30 October 2015 at Cadila Healthcare Limited, Ahmedabad, Gujarat, India as part of the WHO Prequalification Vaccine evaluation and monitoring process.

A Notice of Concern (NOC) was therefore issued to the company. The company immediately stopped production, initiated an internal investigation and initiated a voluntary recall of all the batches of its Lyssavac-N® anti-rabies vaccine manufactured after April 2015, from when investigation revealed the critical issue could have started. The company has also informed WHO that the suspended manufacturing activities for vaccines and biologicals at this site will only resume after acceptable corrective and preventative actions (CAPA) have been submitted, assessed and effectively implemented as confirmed through an onsite inspection.


The full notice of concern is available at www.who.int/entity/immunization_standards/vaccine_quality/NOC_CadilaFebruary2016.pdf?ua=1.
Falsified product alerts

It is necessary to ensure that all medical products are obtained from authentic and reliable sources. Their authenticity and origin should be carefully checked and verified with manufacturers before use. WHO requests increased vigilance for the supply chains of countries likely to be affected by the falsified products mentioned below.

Phenobarbitone

Falsified phenobarbitone tablets circulating in West Africa

This Medical Product Alert relates to the circulation of falsified versions of phenobarbitone (also known as phenobarbital) in West Africa. Phenobarbital is used as a treatment against epilepsy and is frequently dispensed free of charge in community-care health centres.

In December 2015, the Liberia Medicines and Health Products Regulatory Authority (LMHRA) notified WHO of two suspect products that supposedly contain tablets of 100 mg of phenobarbitone. These products were detected through a lack of efficacy (patients treated for epilepsy had an increased recurrence of seizures during the course of their treatment with these products).

Product Name: Phenobarbitone
Batch Number: 2081
Manufacturing Date: 7-2012
Expiry Date: 6-2016
Manufacturer: Mejoc Pharm and Chemical

The manufacturer name only appears on one of the two types of containers shown in the photographs included in the WHO Medical product alert. The name and address of the manufacturer does not exist, and the labelling contains spelling errors.

Investigation of the WHO SSFFC Medical Products database identified that a similar product was found in Guinea Bissau in 2013, with almost identical packaging and labelling and bearing the same batch number, a manufacturing date of 7-2010 and an expiry date of 6-2014. The packaging also contains spelling mistakes. A photograph is provided in the WHO medical product alert.

The product found in Guinea Bissau was tested by an independent laboratory, and analysis indicated that the product contained no active pharmaceutical ingredient. Authorities in Guinea Bissau had been notified. This product was also detected through a lack of efficacy (patients treated for epilepsy had an increased recurrence of seizures during the course of their treatment with these products).

► WHO. Medical Product Alert N° 1/2016, 5 February 2016 (includes photographs).

Yellow fever vaccines

Falsified AMARIL yellow fever vaccines circulating in South East Asia

This Medical Product Alert relates to the confirmed circulation of falsified versions of “AMARIL stabilised vaccine” in South East Asia.

This vaccine is used to immunise against yellow fever and is a WHO-prequalified product. Yellow fever vaccine is on the WHO list of Essential Medicines. On 9 February 2016, the Pasteur Institute in Dakar, Senegal, informed WHO that they had identified a falsified version of their “AMARIL stabilised vaccine” circulating in Bangladesh.
Genuine AMARIL vaccines and solvents are manufactured by the Pasteur Institute in Dakar, Senegal. The Pasteur Institute in Dakar has confirmed that there are a number of falsified elements on the packaging, including a falsified expiry date, as well as other inconsistencies that were identified through visual inspection of photographs of the falsified products as compared to the genuine products. Laboratory analysis is pending.

Product Name: AMARIL stabilised yellow fever vaccine
Batch Number: 2265
Expiry Date: June 2017
Stated manufacturer: Pasteur Institute in Dakar

No serious adverse reactions attributed to this falsified vaccine have been reported at this stage.

► WHO. Medical Product Alert N° 2/2016, 11 February 2016 (includes photographs).

Hepatitis C medicines

Falsified Hepatitis C medicines circulating in South East Asia
This Medical Product Alert relates to the circulation of confirmed falsified versions of Sofosbuvir 400mg + Ledipasvir 90mg and Daclatasvir 60mg in South East Asia. Both products are used to treat Hepatitis C. Daclatasvir 30mg and the fixed dose combination of Sofosbuvir 400mg + Ledipasvir 90mg are on the WHO list of Essential Medicines.

In February 2016, WHO was informed by a local NGO working in Myanmar that they had identified falsified versions of the following two products:

- Product Name: LEDSO capsules DAKAVIR
- Batch Number: 0022 0322
- Expiry Date: 4/2017 4/2017
- Date of manufacture: 5/2015 5/2015

Both products claim to be manufactured by PHARCO Corporation, Alexandria, Egypt.

Laboratory analysis is pending so as to better assess the threat posed to public health. PHARCO Corporation has stated that:
- they do not manufacture the specific fixed dose combination of Sofosbuvir 400mg + Ledipasvir 90mg
- they do not manufacture any products under the names of LEDSO or DAKAVIR
- they do not manufacture Daclatasvir 60mg at this moment in time.

No serious adverse reactions attributed to these falsified products have been reported at this stage.


Swissmedic warns about falsified Harvoni® packs
Switzerland – The Swiss Agency for Therapeutic Products Swissmedic has warned that falsified packs of the hepatitis C medicine Harvoni® have been discovered in Israel. The plastic bottles, which originate in India, were imported via a Swiss trading company and contain white instead of genuine yellow film-coated tablets. Swissmedic is working with other European authorities to establish whether falsified Harvoni® packs have also been imported into other countries.

► Swissmedic Announcement, 4 March 2016.