Safety news

Safety warnings

Loperamide: Serious heart problems with high doses
United States of America – The FDA has warned that higher than recommended doses of the anti-diarrhoea medicine loperamide (Imodium® and associated names), including through abuse or misuse, can cause serious and potentially fatal heart problems. The maximum FDA-approved doses for adults are 8 mg per day for over-the-counter use and 16 mg per day for prescription use. The risk may be increased when high doses of loperamide are taken with medicines that inhibit CYP3A4, CYP2C8, and/or P-glycoprotein.

Health professionals should make their patients aware of this risk and should instruct them to seek medical attention immediately if they experience symptoms of heart problems. Loperamide toxicity should be suspected in case of unexplained QT interval prolongation, torsades de pointes or other ventricular arrhythmias, syncope and cardiac arrest. In such cases loperamide should promptly be discontinued and necessary therapy started. For some cases of torsades de pointes in which drug treatment is ineffective, electrical pacing or cardioversion may be required.

FDA Drug safety communication, 7 June 2016.

Saxagliptin, alogliptin: heart failure
United States of America – An FDA safety review has found that type 2 diabetes medicines containing saxagliptin (Onglyza®, Kombiglyze®) and alogliptin (Nesina®, Kazano®, Oseni®) may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. New warnings have been added to the product information for these medicines. Health care professionals should consider discontinuing saxagliptin- or alogliptin-containing medicines in patients who develop heart failure, and should monitor their diabetes control to see whether other antidiabetic medicines are required. (1)

The EU product information for saxagliptin-containing medicines states that caution is warranted in patients with risk factors such as a history of heart failure or moderate to severe renal impairment. It also states that patients should be advised of the characteristic symptoms of heart failure and to report such symptoms immediately to their health care professionals. For alogliptin the EU product information includes a warning that experience of alogliptin use in clinical trials in patients with moderate to severe congestive heart failure is limited and caution is warranted in these patients. (2)

FDA Drug safety communication, 5 April 2016.

EMA Product information for Vipidia®, Annex 1: Summary of product characteristics, last updated 3 February 2015.
Fluconazole: risk of miscarriage
United States of America – The FDA is evaluating the results of a Danish study that point to a possible increased risk of miscarriage with the use of oral fluconazole (Diflucan® and generics), an antifungal medicine used to treat yeast infections. The Agency is also reviewing additional data. Guidelines issued by the U.S. Centers for Disease Control and Prevention (CDC) recommend only topical – not oral – antifungal products in pregnant women, even in case of persisting or recurring infections that necessitate prolonged treatment. The current FDA product information states that data available from human studies suggest no increased risk in pregnant women exposed to a single 150 mg dose of oral fluconazole. However, high doses (400-800 mg/day) taken repeatedly have resulted in reports of abnormalities at birth. In the Danish study, most of the oral fluconazole use appeared to be one or two doses of 150 mg. Until the review is complete, the FDA advises cautious prescribing of oral fluconazole in pregnancy. (1)

The prescribing information for fluconazole-containing medicines in the EU cautions against use during pregnancy. This is based on reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers received long-term treatment with high doses of fluconazole for fungal infections. (2)

Imatinib, dasatinib, nilotinib, bosutinib, ponatinib: hepatitis B reactivation
European Union, Canada – New wording has been included in product information for products containing BCR-ABL tyrosine kinase inhibitors (including imatinib, dasatinib, nilotinib, bosutinib and ponatinib) to warn about the risk of hepatitis B reactivation in patients who are chronic carriers of this virus. Some reported cases have resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

BCR-ABL tyrosine kinase inhibitors are approved in the EU to treat certain forms of leukaemia, lymphoma and other conditions. Patients should be tested for hepatitis B virus infection before treatment with a BCR-ABL tyrosine kinase inhibitor is initiated. Patients carrying the hepatitis B virus who need treatment should be closely monitored during treatment and for several months thereafter.

Trametinib: gastrointestinal perforation and colitis
United Kingdom – Following a review of data on trametinib (Mekinist®) by European regulators, the MHRA has advised health professionals to use this medicine with caution in patients with risk factors for gastrointestinal perforation, such as gastrointestinal metastases, diverticulitis or concomitant use of medicines that can cause gastrointestinal perforation. Patients should be advised

(1) FDA Drug safety communication, 26 April 2016.
(2) Diflucan® 150 mg capsules. Summary of product information. Last updated on UK electronic Medicines Compendium (eMC) on 6 November 2015.
to seek urgent medical attention if they develop severe abdominal pain.

Trametinib is authorized in Europe either as monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.


**Aflibercept: osteonecrosis of the jaw**

*United Kingdom* – The MHRA has advised that a dental examination and appropriate preventive dentistry should be considered before starting treatment with the anti-cancer medicine aflibercept (Zaltrap®). During treatment, patients should maintain good oral hygiene; receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain or swelling to their health care provider.

This follows reports of cases of osteonecrosis of the jaw in patients who have been treated with aflibercept. Patients who have received prior or concurrent treatment with an intravenous bisphosphonate may be at particular risk. In these patients, invasive dental procedures should be avoided where possible.

Aflibercept is also the active ingredient in Eylea® intravitreal injection, which is authorized for treatment of macular degeneration. Osteonecrosis of the jaw has not been identified as a risk associated with Eylea®.


**Idelalisib: infections and other serious adverse events**

Following observations of serious adverse events – mostly infections – in clinical trials involving the cancer medicine idelalisib (Zydelig®) several regulatory safety reviews have been initiated (see page 208), and the following announcements have been made.

*European Union* – The EMA has recommended new interim safety measures for idelalisib. All patients should receive prophylaxis for *Pneumocystis jirovecii* pneumonia during treatment and should be monitored for respiratory signs and symptoms and for cytomegalovirus infection. Patients should be monitored for neutropenia. In case of moderate or severe neutropenia treatment may need to be interrupted. Idelalisib should not be started in patients with an ongoing systemic infection, or in previously untreated patients with chronic lymphocytic leukaemia (CLL) whose cancer cells have certain genetic mutations. Ongoing first-line treatment for CLL should only be continued if the benefits outweigh the risks for the individual patient. (1)

*United States of America* – The FDA has reminded health professionals that idelalisib is not approved in the United States for previously untreated CLL. (2)

*Canada* – Health Canada has recommended that idelalisib should not be used for first line treatment of CLL. The product monograph will be updated to reflect this new information. (3)

(2) FDA Drug alert, 14 March 2016.
(3) Health Canada Advisory, 3 May 2016.
Thalidomide: viral reactivation and pulmonary hypertension
European Union – Product information for the anti-myeloma medicine thalidomide is being updated to include warnings on the risk of viral reactivation and pulmonary hypertension. Information for healthcare professionals is scheduled to be disseminated in late June 2016.

Cases of viral reactivation, including some serious cases, have been reported following treatment with thalidomide, particularly in patients previously infected with the herpes zoster or hepatitis B viruses. Recommendations to mitigate this risk are similar to those for pomalidomide (see below).

Cases of pulmonary hypertension, including some fatal cases, have also been reported following treatment with thalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease before and during thalidomide therapy.

► EMA Opinions on safety variations/PSURs. EMA/76604/2016. 27 May 2016.

Pomalidomide: hepatitis B reactivation
United Kingdom – A review of clinical studies and reported suspected adverse drug reactions by European medicines regulators has concluded that pomalidomide (Imnovid®) can cause hepatitis B reactivation. Hepatitis B virus status should be established before starting treatment with pomalidomide. If a patient tests positive, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Previously infected patients should be closely monitored for signs and symptoms of active infection throughout pomalidomide treatment.

Pomalidomide in combination with dexamethasone is used to treat adult patients with relapsed and refractory multiple myeloma. Cases of hepatitis B reactivation, some of which progressed to hepatic failure, have been reported in less than 1 of 1,000 patients treated, with most reports occurring during the first treatment cycle.


Olanzapine: rare but serious skin reactions
United States of America – The FDA has warned health professionals and the public that the antipsychotic medicine olanzapine (Zyprexa®, Zyprexa Zydis®, Zyprexa Relprev®, Symbyax® and generics) can cause a rare but serious and potentially fatal skin reaction known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). A new warning has been added to the product information for all olanzapine-containing products.

Olanzapine is used to treat schizophrenia and bipolar disorder. Prescribers should explain the signs and symptoms of severe skin reactions to their patients and instruct them to seek medical care if they develop a fever with a rash and swollen lymph glands, or swelling in the face. Health professionals should stop treatment with olanzapine immediately if DRESS is suspected. (1)

European Union – European medicines regulatory authorities have reviewed cases of DRESS in patients taking olanzapine. An update of the product information for olanzapine-containing medicines has been recommended to list DRESS as a possible side effect. The
condition is very rare and will be listed in the product information as occurring at an unknown frequency. (2)

► (1) FDA Drug safety communication, 10 May 2016.

(2) EMA. New product information wording – Extracts from PRAC recommendations on signals. EMA/PRAC/259913/2016, 28 April 2016.

Known risks

Metformin: expansion of use in kidney impairment

United States of America – The FDA has reviewed available data and has expanded the use of the anti-diabetic medicine metformin to patients with mild renal impairment and certain patients with moderate renal impairment. Metformin was previously contraindicated in the U.S. in all patients with renal impairment because of the risk of lactic acidosis.

The FDA recommends that the glomerular filtration rate-estimating equation (eGFR), rather than the blood creatinine concentration, should be used to assess kidney function. Metformin is contraindicated in patients with an eGFR <30 mL/minute/1.73 m², and is not recommended in patients with an eGFR of 30-45 mL/minute/1.73 m². The eGFR should be monitored at least annually, and more often in patients at increased risk of renal impairment. Metformin should be stopped if the eGFR falls below 30 mL/minute/1.73 m², and treatment discontinuation considered if it falls below 45 mL/minute/1.73 m².

If an iodinated contrast imaging procedure is to be performed in certain at-risk patients, health professionals should stop metformin, re-evaluate the eGFR 48 hours after the procedure, and re-start metformin if renal function is stable.

► FDA Drug safety communication, 10 May 2016.

Aspirin-containing antacids: serious bleeding

United States of America – The FDA has warned consumers about the risk of serious bleeding when using over-the-counter aspirin-containing antacid products. Despite existing warnings in the product information, reports continue to be received of these serious adverse events. The FDA plans to convene an advisory committee of external experts to advise on whether additional regulatory actions are needed.

► FDA Drug safety communication, 6 June 2016.

Oral ketoconazole: use only for serious fungal infections

United States of America – The FDA has reminded health care professionals not to prescribe oral dosage forms of the antifungal medicine ketoconazole (Nizoral® and other names) for skin and nail fungal infections. Since 2013 oral ketoconazole is no longer approved to treat these conditions as it carries a risk of serious liver damage, adrenal gland problems and harmful interactions with other medicines and has been linked to one patient death since the labelling change. Oral ketoconazole should be used only for serious fungal infections when no other effective therapy is available. Yet, a 2015 safety review found that ketoconazole tablets continue to be prescribed for skin and nail fungal infections.

► FDA Drug safety communication, 19 May 2016.
Opioids: enhanced warnings

United States of America – The FDA has announced new class-wide warnings for immediate-release opioid pain medications related to risks of misuse, abuse, addiction, overdose and death, and a warning that chronic use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening for the infant if not recognized and treated.

New safety warnings have also been added to all prescription opioid medications to inform prescribers and patients of additional risks related to opioid use. Clearer information has been included about the indications, dosage, interactions with other medicines including the risk of serotonin syndrome, and about the effects of opioids on the endocrine system, including adrenal insufficiency and androgen deficiency.


Aripiprazole: impulse control disorders

United States of America – The FDA has approved changes to the product information of the mental health drug aripiprazole (Abilify®, Abilify Maintena®, Aristada®) to warn about compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex reported with this medicine. Patients should be informed of these risks and closely monitored. (1)

This follows a similar risk communication issued by Health Canada in 2015 (2).

Product information approved in the EU (3) lists pathological gambling as a side effect which can occur in patients who have no history of gambling, and advises that patients treated with this medicine who have a history of pathological gambling should be monitored carefully.

Altered or increased sexual interest (in up to 1 in 100 people) and weight gain are also listed as side effects.

► (1) FDA Drug safety communication, 3 May 2016.
(2) Health Canada Advisory, 2 November 2015.
(3) EMA Product information for Abilify®, Annex 1: Summary of product characteristics, updated 23 May 2016.

Restrictions

Fluoroquinolones: restricted use in certain uncomplicated infections

United States of America – The FDA has approved labelling changes for fluoroquinolone antibacterial medicines (moxifloxacin, ofloxacin, ciprofloxacin) to limit their use in sinusitis, bronchitis and uncomplicated urinary infection. In treating these conditions, systemic fluoroquinolones should be reserved for patients who do not have alternative treatment options. The reason for this restriction is the risk of a number of disabling and potentially permanent serious side effects that can occur together.

The FDA had communicated safety information about systemic fluoroquinolone drugs in 2008 and 2013. An FDA safety review has shown that systemically used fluoroquinolones are associated with adverse effects that can involve the tendons, muscles, joints, nerves and central nervous system. Health care professionals should stop systemic fluoroquinolone treatment immediately if a patient reports serious side effects and switch to a non-fluoroquinolone antibacterial drug to complete the patient’s treatment course.

► FDA Drug safety communication, 13 May 2016.
Withdrawals from the market

**Meprobamate: last marketing authorization cancelled in U.K.**

**United Kingdom** – Following a 2012 EU-wide review of the sedative medicine meprobamate, the remaining licence holder in the UK has ceased manufacturing and the licence will be cancelled by the end of 2016. *(1)*

In 2012 the EMA had recommended that marketing authorizations for oral medicines containing meprobamate should be suspended in the EU due to serious side effects seen with the medicine *(2)*. The suspension was implemented gradually to avoid the risk of severe withdrawal symptoms in patients stopping treatment abruptly.

► *(1)* MHRA Drug Safety Update vol 9 issue 9, April 2016: 8.


**Fusafungin-containing sprays: rare but serious allergic reactions**

**European Union** – The EMA’s Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed a recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC) to revoke the marketing authorizations for fusafungine-containing products in the EU.

Fusafungine is an antibiotic and anti-inflammatory used in nose and mouth sprays to treat upper airway infections including common cold. The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has found that fusafungin-containing sprays can cause rare but serious, potentially life-threatening allergic reactions, and no measures have been identified to sufficiently reduce or manage this risk. The evidence of beneficial effects of fusafungine is weak. Taking into account the mild and self-limiting nature of upper airway infections such as rhinopharyngitis, the benefits of fusafungine were not considered to outweigh the risks. In addition, it could not be ruled out that fusafungine may promote antibiotic resistance.

► EMA Press release, 1 April 2016.

**Veterinary drug carbadox: to be removed from the U.S. market**

**United States of America** – The FDA has taken steps towards rescinding its approval of the use of the veterinary drug carbadox to treat pigs, because the drug may leave trace amounts of a carcinogenic residue. A preliminary risk characterization had indicated that there could be a potential risk to human health from ingesting pork, especially pork liver, derived from carbadox-treated pigs.

Carbadox was first approved in the U.S. in the early 1970s to control swine dysentery and bacterial swine enteritis. It has also been used to promote weight gain and feed efficiency.

► FDA News release, 8 April 2016.

**Unchanged recommendations**

**Recombinant factor VIII products: no difference in risk of antibody formation**

**European Union** – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has published a summary report of a meta-analysis designed to assess the risk of inhibitors (antibodies) against individual recombinant factor VIII products developing in previously untreated
patients with severe haemophilia A. Specifically, the review concluded that overall, the currently available evidence does not confirm an increased risk associated with Kogenate® Bayer/ Helixate® NexGen, compared with other products. The conclusions are consistent with those of a 2013 PRAC review of Kogenate® Bayer/Helixate® NexGen.
► EMA News, 13 May 2016.

**Meningococcal vaccine: no new safety concerns**

Australia – The TGA has been closely monitoring reports of adverse events following immunisation with Bexsero® meningococcal B vaccine, specifically those relating to fever in infants and children. Fever is a potential risk factor for the development of a seizure. The TGA’s monitoring activities have found no new or unexpected safety issues. All the adverse events observed during the monitoring were identified in the pre-market evaluation, and the numbers of reports were within expectations. Health professionals have been reminded that the Australian Technical Advisory Group on Immunisation has recommended the prophylactic use of paracetamol with every dose of Bexsero® administered to children less than two years old.
► TGA final update, 22 March 2016.

**Inhaled corticosteroids for COPD**

European Union – The EMA has reviewed the known risk of pneumonia with inhaled corticosteroids for chronic obstructive pulmonary disease (COPD). The review concluded that the benefits of these medicines continue to outweigh their well-known risk of pneumonia, which occurs in 1–10 of 100 patients treated. No conclusive evidence was found of any differences in the risk of pneumonia between products. No changes are recommended in the use of inhaled corticosteroids to treat COPD. Health professionals should however be vigilant for signs and symptoms of pneumonia, which overlap with those of exacerbations of COPD.
► EMA Press release, 29 April 2016.
## Medicines safety reviews started

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<td>Placed on New Zealand early warning monitoring scheme due to possible safety concern regarding depression and suicidality, suggested by reports in the WHO database.</td>
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<td><strong>Fluconazole Diflucan® and generics</strong></td>
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<td><strong>Direct-acting antivirals for hepatitis C</strong> (Exviera®, Harvoni®, Olysio®, Sovaldi® and Viekirax®)</td>
<td>Treatment of chronic hepatitis C infection</td>
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<td>◀ EMA Article 20 referral - Review started, 18 March 2016. PMDA Summary of investigation results, 18 May 2016.</td>
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Continued
Non-compliance with good practices

**Alkem Bioequivalence Centre, India**

European Union – The EMA has started a review of medicines for which studies have been conducted at the Alkem Laboratories Ltd site in Taloja, Mumbai, India. This follows a good clinical practice (GCP) inspection of this site which raised concerns regarding study data used to support the marketing authorization applications of some medicines in the EU. The inspection was carried out jointly by the German and Dutch authorities in March 2015 in the context of a routine evaluation of applications for nationally authorized medicines. The EMA will now determine which medicines are concerned and will review the available data to determine whether any action is necessary to protect public health.

► EMA Article 31 referral - Review started, 1 April 2016.

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**Semler Research Center Pvt Ltd, India**

Geneva – The WHO Prequalification Team (PQT) has issued a notice of concern about serious observations made during an inspection of Semler Research Center’s JP Nagar site and Sakar Nagar clinical unit on 27–31 January 2015 and a follow-up inspection on 2-5 December 2015, stating that some of the observations are indicative of manipulation of several studies over an extended period of time. Manufacturers of affected prequalified products have been asked to submit risk assessments with proposed corrective and preventive actions within 30 days (1).

United States of America – The FDA has notified pharmaceutical companies that clinical and bioanalytical studies conducted by Semler Research Center Pvt Ltd in Bangalore, India, are unacceptable.
and need to be repeated. The notification was made as a result of an FDA inspection of Semler’s bioanalytical facility on 29 September–9 October 2015, which found significant instances of misconduct including the substitution and manipulation of study subject samples. (2)

European Union – The EMA has started a review of medicines for which studies have been conducted at Semler Research Centre Private Ltd, as the findings from the FDA and WHO inspections call into question the reliability of data generated at Semler, including data used to support marketing authorization applications in the EU. (3)

► (1) WHO Notice of Concern, 12 April 2016.
(2) FDA Notification to pharmaceutical companies, 20 April 2016.
(3) EMA. Semler – Article 31 review started. 29 April 2016.

Anuh Pharma API manufacturing site, India

Geneva – The WHO Prequalification team has temporarily de-listed two prequalified active pharmaceutical ingredients (API) manufactured by Anuh Pharma Ltd at its facility in Boisar, India (1). This follows a statement of non-compliance with good manufacturing practice (GMP) issued by the French medicines regulatory authority (2). Anuh Pharma has requested WHO to conduct an inspection to verify GMP compliance at the site.

WHO has advised finished product manufacturers to undertake a risk analysis of API batches already purchased, and to halt sourcing of further batches of pyrazinamide from Anuh Pharma until they are reinstated on the WHO prequalification list. National regulatory agencies and procurers should consider both the specific risk posed by an individual FPP batch and the need to maintain continuity of supply.

(2) GMP certificates and non-compliance reports issued by medicines regulatory authorities in the European Economic Area (EEA) are publicly available at: http://eudragmdp.ema.europa.eu/inspections/gmpc/index.do

Falsified product alert

Injectable carmustine

United States of America – The FDA has warned health professionals that a falsified version of the FDA-approved cancer drug carmustine for injection 100 mg (BiCNU®) has been detected in some countries outside the U.S. The authentic product is approved in the U.S. to treat different types of brain cancer, multiple myeloma, and lymphoma (Hodgkin’s and non-Hodgkin’s). The genuine product is manufactured by Emcure Pharmaceuticals Ltd.

The product is available as a vial of BiCNU® and dehydrated alcohol co-packaged together. The best way to distinguish the genuine from the falsified product is to look at the BiCNU® vial inside the packaging. The authentic product has a blue flip top while the falsified product has a grey flip top. The National Drug Code (NDC) number on the authentic product vial should end with -31, not -41. Photographs of an authentic and a falsified product, and a list of lot numbers, batch vial, manufacturing dates, and expiration dates found on falsified products, are available on the FDA web site.

► FDA Drug alert, 12 May 2016.
TGA Safety advisory, 23 May 2016.