Safety news

Unchanged recommendations

**Olmesartan in diabetic patients: no increased cardiovascular risk**

**United States of America** – The U.S. Food and Drug Administration (FDA) has found no clear evidence of increased cardiovascular risks associated with the use of the blood pressure medication olmesartan in diabetic patients. FDA recommendations for the use of olmesartan will remain the same, but information about some of the studies will be included in the product labels.

The safety review was prompted by an unexpected finding of increased risk of cardiovascular death with olmesartan compared to placebo in a clinical trial in patients with type 2 diabetes.

► **FDA Safety announcement, 24 June 2014.**

**Levonorgestrel and ulipristal emergency contraceptives: suitable for all bodyweights**

**European Union** – The European Medicines Agency (EMA) advises that emergency contraceptives containing levonorgestrel or ulipristal acetate can continue to be used in women of all weights.

An EU-wide review had been triggered by a change to product information for a levonorgestrel-containing contraceptive in an EU country, stating that the product was less effective in women above 75 kg and not effective in women above 80 kg. The review did not confirm that high bodyweight reduces the contraceptive effect.

► **EMA Press release, 24 July 2014.**

Restricted use

**Bromocriptine: post-partum suppression of lactation only for compelling reasons**

**European Union** – The EMA has advised against the routine use of bromocriptine-containing medicines to stop lactation or to relieve pain or swelling of the breasts after childbirth.

Due to a risk of rare but potentially serious cardiovascular, neurological and psychiatric side effects, bromocriptine-containing medicines should only be used (in strengths up to 2.5 mg) to stop lactation when there are compelling medical reasons, such as avoiding further distress after loss of the baby during or just after childbirth, or in mothers with HIV infection, who should not breastfeed.

Bromocriptine must not be used in women with disorders that increase blood pressure, a history of coronary artery disease or other severe cardiovascular conditions, or a history of severe psychiatric disorders.

► **EMA Press release, 21 August 2014.**

**Ferumoxytol: hypersensitivity reactions**

**European Union** – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that the benefits of ferumoxytol (Rienso®), used to treat anaemia in patients with
long-term kidney disease, continue to outweigh the risks. Considering recent reports of serious hypersensitivity reactions, the Committee recommended that ferumoxytol should be given by infusion over at least 15 minutes (instead of by injection), and that it should be contraindicated in patients with any known history of drug allergy.

EMA. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7-10 July 2014.

Canada – Health Canada has endorsed new safety information on ferumoxytol (Feraheme®), and the product information has been revised to reflect new usage restrictions. Ferumoxytol is now contraindicated in patients with any allergy to other parenteral iron products or with two or more drug allergies. The product should be administered with special precautions to mitigate the risk of anaphylaxis and other hypersensitivity reactions.


Intravenous ondansetron: dosage restrictions in patients over 65

Canada – The manufacturer, in consultation with Health Canada, has recommended dosing restrictions for intravenous (IV) ondansetron (Zofran®) in patients above 65 years of age. The same action had been taken earlier by the FDA and the EMA to mitigate the risk of QT prolongation, which can lead to potentially life-threatening heart arrhythmia.

In patients aged 75 years or more the initial IV dose of ondansetron must not exceed 8 mg, while in patients aged 65 to under 75 years it must not exceed 16 mg. Subsequent IV doses must not exceed 8 mg and may be given 4 and 8 hours after the initial dose. All IV doses must be diluted in 50–100 mL of saline or other compatible fluid and infused over no less than 15 minutes. The product information has been updated. – There are no changes to the recommended oral dosing.

Health Canada also reminds health professionals that in patients over 65 years of age ondansetron should be used only to prevent chemotherapy-associated (but not post-operative) nausea and vomiting.

Health Canada Advisory, 12 June 2014.

Influenza vaccine (Fluvax®): not to be used in children under five

Australia – The company bioCSL has published its research into fever and fever-related convulsions that occurred with its influenza vaccine (Fluvax®) in 2010 in children under five years of age. These adverse events were most likely caused by a stronger immune response due to the introduction of new viral strains in that season’s vaccine, as well as certain extra viral components generated under the standard production method.

The Therapeutic Goods Administration (TGA) has not approved the product for use in children under the age of five. In children aged five to under nine years, health professionals should carefully consider the benefits and risks of vaccinating each individual child with the 2014 bioCSL Fluvax vaccine. The product information has been updated. Additional warnings are also provided on the packaging and for display on vaccine refrigerators.

TGA News, 12 June 2014.
Etonogestrel / ethinyl estradiol vaginal ring: contraindications
Canada – The manufacturer, in consultation with Health Canada, has spelled out new contraindications in the product information of etonogestrel / ethinyl estradiol slow release vaginal ring (Nuvaring®). The product should not be used by women aged over 35 who smoke, or by those who have severe or multiple risk factors for thrombosis, including: valvular heart disease with complications, hypertension, severe dyslipoproteinemia, abnormality in proteins that regulate coagulation, diabetes mellitus with vascular involvement, or major surgery with prolonged immobilization. Neither should the product be used by women who have experienced migraines with focal neurological symptoms, or those who suffer from pancreatitis associated with severe hypertriglyceridaemia.

In November 2013 the EMA had advised against using combined hormonal contraceptives in women with one severe risk factor, or multiple risk factors, for blood clots.


Safety warnings

Lidocaine oral viscous solution: not to be used in teething pain
United States of America – The FDA has warned that oral viscous lidocaine 2 percent solution should not be used to treat teething pain, an indication for which the medicine is not approved in the United States.

Overdosing or accidental ingestion of lidocaine can cause seizures, severe brain injury, heart problems and death. The FDA is requiring a new Boxed Warning and revisions to the Warnings and Dosage and Administration sections of the product label to highlight this information.

More generally, the FDA advises parents and caregivers not to use over-the-counter topical medications for teething pain. A 2011 communication had warned against benzocaine gels as they can cause methaemoglobinaemia, a rare but life-threatening adverse effect decreasing the amount of oxygen carried through the blood. Instead, teething pain can be relieved by using a chilled (not frozen) teething ring, and by gently rubbing or massaging the child’s gums with a finger.

► FDA Safety announcement, 26 June 2014.

Terconazole cream: rare but serious allergic reactions
Canada – The manufacturer, in consultation with Health Canada, has informed the public that very rare but serious or even life-threatening adverse reactions of anaphylaxis or toxic epidermal necrolysis have been reported during treatment with terconazole vaginal cream (Terazol®). The product is approved for the local treatment of vulvovaginal candidiasis (moniliasis). The Canadian product monograph has been updated to include this new safety information.

Patients should be counseled about these risks, and should be instructed to discontinue use of the medicine if signs of serious allergic reactions occur.

► Health Canada Advisory, 9 June 2014.

Docetaxel: alcohol intoxication
United States of America – The FDA warns that the intravenous chemotherapy medicine docetaxel contains alcohol, which may cause patients to experience intoxication or feel drunk during and after treatment. Some medications, such as
pain relievers and sleep aids, may worsen these effects.

Patients should avoid driving, operating machinery or performing other activities that require alertness for one to two hours after infusion of docetaxel. Health care professionals should consider the alcohol content of the specific docetaxel-containing product when prescribing or administering the medicine to patients, and should monitor and counsel patients appropriately. The FDA is revising the labels of all docetaxel-containing products to warn about this risk.

Topical acne products: rare but serious hypersensitivity reactions

United States of America – The FDA is warning that certain over-the-counter topical acne products containing benzoyl peroxide or salicylic acid can cause rare but serious and potentially life-threatening allergic reactions. These products are available as gels, lotions, face washes, solutions, cleansing pads, toners, face scrubs and other products under various brand names.

Consumers should stop using the product and seek emergency medical attention immediately if they experience throat tightness, difficulty breathing, feeling faint, or swelling of the eyes, face, lips or tongue. Consumers should also stop using the product if they develop hives or itching. The reactions may occur within minutes to a day or longer after product use. They differ from local skin irritations at the product application site, such as redness, burning, dryness, itching, peeling or slight swelling, that are already included in the product labels.

The FDA is encouraging manufacturers to include directions on the product labels, instructing consumers to apply a small amount to a small affected skin area for three days before using a topical acne product for the first time. The product should only be used if no discomfort occurs, and if the consumer has not previously experienced adverse reactions to it.

Testosterone: heart and blood vessel problems

Canada – Health Canada has completed a safety review on testosterone replacement products, and has found a growing body of evidence from various sources for serious and possible life-threatening heart and blood vessel problems with the use of these products.

The agency reminds health professionals that testosterone products should only be used to treat low testosterone levels in men as confirmed by laboratory testing. Patients should be assessed for any cardiovascular risk factors or past events before therapy is initiated, and should be closely monitored thereafter.

Health Canada will continue to work with FDA and EMA to address this safety concern.

Paracetamol: rare but severe skin reactions

New Zealand – Medsafe has warned that paracetamol is associated with a risk of rare but serious skin reactions, as recently communicated by the FDA. Patients should consult their doctor at the first appearance of a skin rash, skin peeling, mouth ulcers, or any sign of hypersensitivity. If serious skin reactions
occur, paracetamol should be stopped immediately.

The New Zealand Centre for Adverse Reactions Monitoring (CARM) has received four reports of serious skin reactions causally associated with paracetamol. These included two reports of erythema multiforme, one of toxic epidermal necrolysis and one of Stevens Johnson Syndrome.

Non-steroidal anti-inflammatory drugs (NSAIDs) can also cause skin reactions. There does not appear to be cross-sensitivity between paracetamol and NSAIDs.

U.S. FDA Safety Announcement, 1 August 2013.
Medsafe. NSAIDs can SCAR (Severe Cutaneous Adverse Reaction). Prescriber Update 33(2): 11-12.

Ofatumumab: fatal infusion reaction
Canada / European Union – The manufacturer, in agreement with regulatory authorities, has informed health professionals about a fatal infusion reaction during administration of the first dose of ofatumumab (Arzerra®) to a patient with chronic lymphocytic leukaemia with no known history of cardiac disease.

Even with premedication as prescribed in the product information, severe infusion reactions can still occur. Health care professionals should inform their patients of this risk. If a severe infusion reaction is suspected, the infusion should be stopped immediately and the symptoms should be treated. Ofatumumab should be given under the supervision of an experienced doctor and in an environment with adequate facilities to monitor and treat infusion reactions. The Canadian product information is being updated to include this information.

EU regulatory authorities have reminded health professionals that infusion reactions have also occurred with other anti-CD20 monoclonal antibodies such as rituximab and obinutuzumab. Recommendations to reduce this risk are found in the summary of product characteristics for each product.

► Health Canada advisory, 6 August 2014.
MHRA Drug safety advice, 7 August 2014.

Fentanyl patches: accidental exposure can be life-threatening
European Union – The marketing authorization holders, in agreement with regulatory authorities, have reminded health professionals that accidental exposure to fentanyl patches can cause life-threatening harm, particularly in children. Patients and caregivers should be advised to:
• choose the patch application site carefully (see patient information leaflet);
• check the adhesion of the patch once applied, especially the edges;
• fold the used patch as soon as it is removed so that its adhesive side sticks firmly to itself, then dispose of it safely;
• if a patch is transferred to another person, remove it immediately and seek medical advice; and
• if a patch is swallowed, seek medical help immediately.

The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has performed an EU-wide review. In addition to the above safe handling measures the PRAC has recommended that the visibility of fentanyl patches should be improved.

► MHRA Drug safety message, 18 June 2014.
Sugammadex: ventricular fibrillation, ventricular tachycardia and coronary arteriospasm
Japan – The Pharmaceuticals and Medical Devices Agency of Japan has warned that cases of coronary arteriospasm, ventricular fibrillation and ventricular tachycardia have been reported in patients treated with sugammadex in Japan. The medicine is used to reverse the effect of muscle relaxants vecuronium and rocuronium, which are administered to support mechanical ventilation or intubation during surgery.

The product information already included a warning about the risk of marked bradycardia and/or cardiac arrest after injection of sugammadex. A warning has been added about the above-mentioned adverse effects, which can occur within minutes after administration. Patients should be carefully monitored and appropriate measures taken in case of any abnormalities.

► PMDA Revision of precautions: Sugammadex sodium. 6 August 2014.

Interferon beta products: thrombotic microangiopathy and nephrotic syndrome
European Union – EMA has endorsed new safety information in response to cases of thrombotic microangiopathy (TMA) including fatal cases, and nephrotic syndrome reported with interferon beta used to treat multiple sclerosis. Both conditions may develop weeks or even years after starting treatment.

Health professionals should suspect TMA if they observe thrombocytopenia, new onset hypertension, fever, central nervous system symptoms and impaired renal function, and should confirm the diagnosis based on blood platelet and serum lactate dehydrogenase levels, renal function tests, and red blood cell fragments on a blood film. TMA must be treated promptly (considering plasma exchange), and immediate discontinuation of interferon beta is recommended.

Health professionals should also look out for signs of nephrotic syndrome, especially in patients at high risk of renal disease, treat promptly if it occurs, and consider stopping interferon beta.

► EMA safety information, 24 August 2014.

Topiramate: Visual field defects
New Zealand – The manufacturer, in agreement with Medsafe, has informed health professionals that visual field defects have been reported in patients receiving topiramate tablets, independently of elevated intraocular pressure. In clinical trials, most of these events were reversible after topiramate discontinuation. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the medicine.

► Medsafe Safety information, 5 August 2014.

Suspended
Methadone with high molecular weight povidone: to be reformulated
European Union – The EMA has endorsed the recommendation to suspend the marketing authorization for oral methadone solutions containing high molecular weight povidone until they have been reformulated to prevent abuse. Methadone tablets that contain low molecular weight povidone will remain on
the market with changes to the product information to reinforce the message that tablets are for oral administration only.

Methadone is used in rehabilitation programmes to prevent or reduce withdrawal symptoms in people dependent on opioids. Some patients misuse oral methadone solutions by injecting them into a vein. The povidone is then not easily excreted from the body and accumulates inside the cells of vital organs, which may cause serious harm.


### Overview of safety reviews started

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<td>Cardiovascular risk with high dose regimen (2 400 mg per day) taken over long periods; possible interactions with low-dose aspirin (taken to reduce the risk of heart attacks and strokes)</td>
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<td>Ivabradine (Coralan®)</td>
<td>Treatment of heart failure and stable angina</td>
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### Medicines quality issues

#### Update on anti-cancer medicines stolen in Italy

European Union – The investigation of the supply of stolen vials of pemetrexed, trastuzumab and infliximab has identified two additional products – bevacizumab and rituximab – that have been distributed illegally from Italy. A document is available on the EMA website that lists the batches concerned by the investigation. EMA had announced the theft on 16 and 17 April 2014.

► EMA News, 3 June 2014.

#### EMA reinstates GMP certificate for Ranbaxy’s Toansa site

European regulatory authorities have finalized their assessment of reported non-compliance with Good Manufacturing Practice (GMP) at Ranbaxy Laboratories’ manufacturing site in Toansa, India, and have concluded that the deficiencies do not pose a risk to public health. The EU authorities will therefore reinstate the GMP certificate which was suspended in January 2014.

The assessment followed an FDA inspection which had revealed areas of non-compliance with GMP at the site. An international team of inspectors conducted an unannounced inspection and found that the manufacturer has taken appropriate corrective and preventive measures. In
addition, samples of the medicines on the EU market were tested and found to meet the approved quality specifications.

European regulatory authorities will continue watching the Toansa site closely in collaboration with their counterparts in India and around the globe.

► EMA Press release, 5 June 2014.

Compounded products from two U.S. facilities may not be sterile

United States of America – The FDA has alerted health care professionals not to use medicines marketed as sterile produced by two compounders, namely Downing Labs LLC, also known as NuVision Pharmacy, and Unique Pharmaceuticals Ltd.

FDA inspections at the facilities have revealed insanitary conditions, resulting in a lack of sterility of the products and putting patients at risk of infection.

Compounding operations have been repeatedly linked to medicines quality problems. The FDA has outlined strengthened expectations for this type of manufacturing (see page 333).

► FDA Drug alert, 18 July 2014.

Micro Labs Hosur manufacturing site gets WHO notice of concern

Geneva – The WHO Prequalification team has issued a Notice of Concern about Micro Labs Ltd.’s manufacturing site in Hosur, Tamil Nadu, India, following a WHO inspection in February 2014.

If the deficiencies observed during the inspection are not addressed within the recommended time frame, WHO may consider suspending the prequalification of products manufactured at the site, and/or recommend suspending their procurement by UN and other international agencies.

► WHO Prequalification Update, 6 June 2014.

Ipca halts API shipments to the U.S.

India – Ipca Laboratories Ltd has voluntarily suspended shipments of active pharmaceutical ingredients (APIs) to the United States from its manufacturing site at Ratlam after an FDA inspection found non-compliances with Good Manufacturing Practice (GMP). Health Canada then asked Ipca Laboratories to voluntarily stop shipment of products to Canada, and asked Canadian companies to temporarily quarantine any products containing APIs from Ipca. The company is working to address the deficiencies. Neither the FDA nor Health Canada have requested a recall of products already on the market.

WHO has prequalified a number of APIs and finished products which may incorporate APIs manufactured at the Ratlam site. The WHO prequalification programme advises that no issues have been reported that directly impact product quality. It has issued an information note with details of the products concerned, action taken by WHO, and advice to procurement agencies on how to verify that the manufacturers responsible for the products have taken adequate measures to ensure that all batches meet agreed quality standards.

  Health Canada Advisory. 17 September 2014.