Safety news

Unchanged recommendations

Testosterone: cardiac risk not confirmed

European Union – The European Medicines Agency (EMA) has reviewed available data from studies on testosterone-containing medicines, following concerns over serious side effects on the heart and blood vessels. Testosterone is used to treat hypogonadism (lack of testosterone produced by the body) in men. Available data do not provide consistent evidence that the use of testosterone increases the risk of heart problems in these patients, and hypogonadism itself may increase this risk.

The EMA recommended that testosterone-containing medicines should only be used where lack of testosterone has been confirmed by signs and symptoms as well as laboratory tests. The product information for these medicines will be updated to include this recommendation, together with warnings against use in men with severe heart, liver or kidney problems, and information that data on safety and effectiveness in patients over 65 years of age are limited and that age-specific testosterone reference values do not exist.

Clinical studies on the safety of testosterone are still ongoing, and their results will be considered in future regular benefit-risk assessments for these medicines. (1)

New Zealand – Medsafe’s Medicines Adverse Reactions Committee (MARC) has reviewed the available information about cardiovascular risks associated with testosterone therapy, and has found that the evidence of increased cardiovascular risk was not conclusive. The Committee recommended that marketing authorization holders should be requested to update the warnings and precautions section in the product information, and that general articles should be published to raise awareness of this risk. (2)

(1) EMA Press release, 21 November 2014.
(2) Medsafe. Minutes of the 159th Medicines Adverse Reactions Committee Meeting – 11 September 2014.

Agomelatine: strengthened advice to monitor liver function

European Union – The EMA has concluded its regular benefit-risk assessment of agomelatine (Valdoxan®, Thymanax®), used to treat major depression in adults, and has recommended measures to reiterate the importance of liver monitoring, the cornerstone for the safe use of agomelatine.

Agomelatine has a risk of severe side effects on the liver, especially in vulnerable patients. Nevertheless it remains a valuable treatment option in certain situations. Strengthened advice on liver function monitoring will be included in the product information, and a patient booklet will be distributed.

The current product information includes a warning that the medicine should not be used in patients aged 75 years or more. The EMA considered that available data
does not justify upgrading of this warning to a contraindication.
► EMA News, 26 September 2014.

**Restricted use**

**Intravenous nicardipine: only to control high blood pressure in specialist settings**

United Kingdom – In agreement with the Medicines and Healthcare Products Regulatory Agency (MHRA), the marketing authorization holder of an intravenous nicardipine medicine has informed health professionals of the outcomes of a European regulatory review of intravenous nicardipine, initiated in 2012 at the request of the MHRA. The EMA had advised that these medicines should only be used to treat acute life-threatening hypertension and post-operative hypertension. Treatment should be administered by a specialist and in a well-controlled environment. Other uses are not recommended.

In adults, continuous infusion should be started at a rate of 3–5 mg/h. The rate can then be increased but should not exceed 15 mg/h, it should gradually be reduced when the target blood pressure is reached. Blood pressure should be monitored continuously during infusion and for at least 12 hours thereafter.
► MHRA Safety Communication, 12 September 2014.

**Bromocriptine: not for pre-menstrual syndrome or benign breast disease**

New Zealand – Medsafe has reviewed data on the efficacy and safety of bromocriptine when used to treat premenstrual symptoms and mastalgia. Available data provide insufficient evidence to recommend bromocriptine use for these indications, and information from its use of similar doses for other indications suggest that bromocriptine may cause fibrosis and impulse control disorders. Medsafe will therefore request the marketing authorization holder of bromocriptine to remove the above indications from the data sheet. (1)

Earlier, Medsafe had made recommendations on the safety and efficacy of bromocriptine for lactation suppression (2) in response to an EMA review started on the subject, and – as mentioned in the previous issue of WHO Drug Information – the EMA had recommended against the routine use of bromocriptine to stop lactation or to relieve pain or swelling of the breasts after childbirth (3).
► (1) Medsafe. Minutes of the 159th Medicines Adverse Reactions Committee Meeting - 11 September 2014.
► (2) Minutes of the 156th Medicines Adverse Reactions Committee Meeting - 5 December 2013.
(3) EMA Press release, 21 August 2014.

**Colistimethate sodium: reserve for serious infections resistant to standard antibiotics**

European Union – Colistinin and colistimethate sodium (known as polymyxins) have been available since the 1960s, but have been in little use until they were brought back in recent years as an option to treat infections resistant to standard antibiotics. The EMA has reviewed the safety and effectiveness of injectable and liquid inhaled products containing colistimethate sodium.
The review concluded that injection or infusion of colistimethate sodium should be reserved for the treatment of serious infections caused by susceptible (i.e. aerobic Gram-negative) bacteria in patients whose other treatment options are limited. The medicine should be given with another suitable antibiotic where possible. Great caution is advised when using intravenous colistimethate sodium together with other medications that are potentially nephrotoxic or neurotoxic.

The Committee recommended that doses should always be expressed in international units (IU) to avoid medication errors, and proposed a conversion table for inclusion in the product information. Despite limited data the Committee recommended doses for use in patients with kidney problems and in children, and provided guidance on dosage for intraventricular or intrathecal or injection in adults, i.e. when the medicine is given directly into fluid surrounding the brain or spinal cord.

Valproate: not to be used in pregnancy
European Union – The EMA has recommended strengthening the restrictions on the use of valproate medicines due to the risk of malformations and developmental problems in children exposed to valproate in the womb.

Valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. Where valproate is the only option, women should use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

In some countries valproate is authorized for the prevention of migraine. Pregnancy should be excluded before starting valproate treatment for migraine, and women should use effective contraception.

The EMA further recommended that educational materials should be provided to all healthcare professionals in the EU and to women who are prescribed valproate to inform them of these risks.

These strengthened restrictions are based on a review of available data as well as consultations with patients, affected families and experts.


Sulfur hexafluoride: not to be used with dobutamine in certain patients
United Kingdom – The marketing authorization holder, in agreement with the EMA and the MHRA, have informed health professionals that rare but severe and sometimes fatal arrhythmias have been reported in patients with cardiovascular instability undergoing stress echocardiography with sulfur hexafluoride (SonoVue®) in combination with dobutamine.

Sulfur hexafluoride is therefore contraindicated in combination with dobutamine in patients with conditions suggesting cardiovascular instability, e.g. recent acute coronary syndrome or clinically unstable ischaemia.

When administered alone, sulfur hexafluoride should be used in such at-risk patients only with extreme caution and after a careful risk/benefit assessment. Vital signs should be closely monitored during and after administration, because in these patients allergy-like and/
or vasodilatory reactions may lead to life-threatening conditions.

Sulfur hexafluoride is a contrast agent used in diagnostic procedures involving echocardiography and Doppler sonography.

► MHRA Safety Information, 1 October 2014.

Safety warnings

Ivabradine: heart problems

European Union – The EMA has completed its review of ivabradine – used to treat heart failure and symptoms of angina – and has made recommendations aimed at reducing the risk of heart attack and bradycardia.

When used for angina, ivabradine should only be started if the patient’s resting heart rate is at least 70 beats per minute. Doctors should consider stopping treatment if there is no or only limited improvement in angina symptoms after three months.

Ivabradine should not be prescribed together with verapamil or diltiazem that reduce the heart rate, and patients should be monitored for atrial fibrillation. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.


Voriconazole: phototoxicity and squamous skin cancer

United Kingdom – The marketing authorization holder, in consultation with the MHRA, has reminded health professionals that voriconazole (Vfend®) is associated with a risk of phototoxicity and skin squamous cell carcinoma. Voriconazole is used for the treatment of worsening, possibly life-threatening fungal infections and prophylaxis of invasive fungal infections in certain transplant recipients.

Health professionals are reminded to adhere to the advice given in the product information. If phototoxic reactions occur, they should refer the patient to a dermatologist and should consider stopping voriconazole treatment. If treatment is continued, the skin should be checked frequently and thoroughly, and voriconazole treatment should be stopped if precancerous skin lesions or squamous cell carcinoma are identified.

Voriconazole is also associated with a risk of liver toxicity. The UK product information (available at www.medicines.org.uk) has been updated with revised advice on monitoring liver function.

► MHRA Drug safety message, 10 October 2014.

Carvedilol: Rare severe skin reactions

New Zealand – The marketing authorization holder of carvedilol (Dilatrend®) has informed health professionals that very rare cases of severe cutaneous adverse reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported during treatment with the product, and that treatment should be permanently discontinued in patients who experience severe cutaneous adverse reactions possibly attributable to this medicine. The product information has been updated accordingly.

► Medsafe Safety information, sent 26 November 2014.
Immunoglobulins: rare but serious risk of blood clots

Canada – Health Canada, in collaboration with marketing authorization holders, has informed health professionals of the risk of thromboembolic events in patients using non-hyperimmune immunoglobulins. Such events can occur regardless of dose or route of administration and in the absence of known risk factors. Canadian product monographs for all non-hyperimmune immunoglobulins (GamaSTAN® S/D, Gammagard Liquid, Gammagard S/D, Gamunex®, Hizentra®, IGIVnex®, Immune Serum Globulin (Human), Octagam® 5%, Octagam® 10%, and Privigen®) were updated to include thromboembolic events in the Serious Warnings and Precautions section.

► Health Canada Advisory, 9 October 2014.

Simeprevir: increased bilirubin may cause serious outcomes

Japan – The Pharmaceutical and Medical Devices Agency (PMDA) has informed health care professionals that eight cases, including three fatal ones, of remarkably increased blood bilirubin in patients treated with simeprevir have been reported in Japan within 10 months following market authorization. Simeprevir is a recently approved medicine used in combination with other medicinal products for the treatment of chronic hepatitis C.

While the risk of increased blood bilirubin levels with simeprevir is known, the three deaths occurred after hepatic dysfunction and renal impairment to which the PMDA considers that hyperbilirubinaemia may have contributed.

The PMDA has requested that the product information should be updated to advise health professionals to test blood bilirubin regularly during simeprevir treatment and to monitor patients carefully even after simeprevir is stopped. Prompt action is important, as measures to avoid serious outcomes may be less effective once jaundice, general malaise and/or other symptoms occur.

► PMDA Investigation results, 24 October 2014.

Basiliximab: cardiac adverse events when used off-label in heart transplants

United Kingdom – In agreement with the EMA and the MHRA, the marketing authorization holder has reminded health professionals that basiliximab (Simulect®) is indicated only for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation. Its efficacy and safety in other transplant indications have not been demonstrated.

In several small clinical trials in heart transplant recipients, serious adverse events such as cardiac arrest, atrial flutter and palpitations have been reported more frequently with basiliximab than with other induction agents. The warnings section of the Summary of Product Characteristics will be updated accordingly.

The communication follows a review by European drug regulatory agencies regarding the off-label use of basiliximab in heart transplants.

► MHRA Drug safety message, 10 October 2014.

Ustekinumab: serious skin conditions

Canada – The marketing authorization holder, in consultation with Health Canada, has informed health professionals about rare reports of exfoliative dermatitis and erythrodermic
psoriasis in psoriasis patients receiving ustekinumab (Stelara®). These skin conditions can occur within a few days of starting treatment, can be severe and can lead to hospitalization. Treatment with ustekinumab should be discontinued if a drug reaction is suspected, and the symptoms should be treated.

Exfoliative dermatitis can appear as redness and shedding of the skin over almost the entire area of the body, which may be itchy or painful. Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis as part of the natural course of their disease.

The product monograph will be updated to reflect this information. (1)

European Union – At its October meeting, the EMA’s Committee for Medicinal Products for Human Use (CHMP) adopted a safety variation to add the risk of serious skin conditions with ustekinumab to the Summary of Product Characteristics. Health professionals in the EU will be informed and the product information will be updated. (2)

(2) EMA/CHMP. Opinions on safety variations/PSURs adopted at the CHMP meeting of 20-23 October 2014.

Ponatinib: blood vessel blockage

European Union – The EMA has reviewed the benefits and risks of ponatinib (Iclusig®) and has recommended to include strengthened warnings about the risk of blood clots or blood vessel blockage in the product information. The risk is likely to be dose-related, although available data are not sufficient to make a formal recommendation on dose reduction.

Ponatinib is authorized for use in patients with chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia who cannot take or tolerate several other medicines of the same class.

The recommended starting dose should remain 45 mg of ponatinib once a day. The cardiovascular status of the patient should be assessed before starting therapy and regularly monitored during treatment.

Healthcare professionals should consider a dose reduction in patients with ‘chronic phase’ CML who are responding well to treatment, and who might be at particular risk of blood vessel blockage. Dose modifications or treatment interruption should be considered to manage treatment toxicity; if a reduced dose is used, patients should be monitored for maintenance of therapeutic response. Ponatinib should be stopped if there has been no response after three months of treatment. Patients should be monitored for high blood pressure or signs of heart problems.

Educational material will be provided to healthcare professionals, and a new study on the safety and benefits at lower doses of the medicine is planned.

► EMA Press release, 24 October 2014.

Diclofenac and other NSAIDs: cardiovascular risks and liver damage

Australia – The Therapeutic Goods Administration (TGA) has reviewed a range of non-steroidal anti-inflammatory drugs (NSAIDs) and has found that the known risks at prescription-only dosages – high blood pressure, heart failure, heart attack and stroke, as well as liver damage in the case of diclofenac – also
apply to over-the-counter (OTC) forms of diclofenac, naproxen and ibuprofen.

While the OTC products are safe at the recommended doses and for short durations, inappropriate use or overuse can pose a significant health risk. The TGA has reminded health professionals of prescribing recommendations for NSAIDs, and has encouraged them to educate patients on the signs and symptoms of serious cardiovascular toxicity and the need to seek medical attention immediately if they occur.

The recommendations are based on a review of cardiovascular risks associated with diclofenac, naproxen, ibuprofen, celecoxib, etoricoxib, indomethacin, meloxicam and piroxicam, as well as a full safety review of diclofenac. The TGA is exploring options to reduce the risks. (1)

Canada – The marketing authorization holders of systemic diclofenac products (Voltaren®, Arthrotec®), in consultation with Health Canada, have informed health professionals that at doses from 150 mg per day these products have a risk of heart problems and stroke that is comparable to that of COX-2 inhibitors (coxibs). The risk may increase with the dose and duration of use.

The maximum recommended daily dose for all indications has been reduced to 100 mg in product information and labelling of diclofenac-containing tablets and suppositories, except for Voltaren Rapide® which allows for a 200 mg dose only on the first day of treatment for dysmenorrhea. The lowest effective dose should be used for the shortest possible duration. COX-2 inhibitors and diclofenac are not recommended in patients with pre-existing cardiovascular disease (CVD) or cerebrovascular disease, or presenting risk factors for CVD. Treatment options other than NSAIDs, particularly COX-2 inhibitors and diclofenac, should be considered first in these patients. (2)

► (1) TGA Safety advisory, 7 October 2014.
(2) Health Canada Advisory, October 6, 2014.

Denosumab: osteonecrosis of the jaw and hypocalcaemia

United Kingdom – The manufacturer, in consultation with regulatory authorities, has warned that denosumab (Prolia®, Xgeva®) is associated with a risk of osteonecrosis of the jaw and hypocalcaemia. Denosumab is used to prevent bone complications in osteoporosis and certain types of cancer.

Treatment should not be started in patients due to undergo, or recovering from, oral surgery. Appropriate preventive dentistry is recommended before patients with risk factors for osteonecrosis of the jaw are given denosumab. During treatment, good oral hygiene and dental check-ups are encouraged.

The risk of hypocalcaemia increases with the degree of renal impairment. Before treatment existing hypocalcaemia must be corrected. Adequate calcium and vitamin D intake is important especially in patients with renal impairment.

Patients should immediately report any pain or swelling in the mouth, loose teeth, as well as any symptoms of hypocalcaemia.

► MHRA. Information sent to healthcare professionals in August about the safety of medicines. 2014.

Pregabalin: liver damage

Japan – The PMDA has informed health professionals that cases of fulminant hepatitis and hepatic dysfunction have
been reported in patients treated with pregabalin in Japan, including cases where causality could not be ruled out. Pregabalin is used for the treatment of neuropathic pain and fibromyalgia. The Agency recommended to revise the package insert to include these adverse events in the section on clinically significant adverse reactions.

While hepatic effects in patients taking pregabalin have also been reported to EU and WHO pharmacovigilance databases, the data do not support the conclusion that these adverse effects are associated with the use of pregabalin specifically.

► PMDA. Summary of investigation results. Pregabalin, 16 September 2014.

Zopiclone: next-day impairment
Canada – The manufacturer, in consultation with Health Canada, has informed health professionals of new dosage recommendations for the sleeping medication zopiclone (Imovane®) to minimize the risk of next-day impairment. This follows recommendations provided by the EMA for zolpidem and by the FDA for eszopiclone (see WHO Drug Information Vol. 28, No. 2, 2014).

The recommended starting dose of zopiclone has been reduced to 3.75 mg (one-half of the 7.5 mg tablet) at bedtime; the lowest effective dose for each patient should be used. The prescribed dose should not exceed 5 mg in elderly patients, in those with hepatic or renal impairment or in those being treated with potent CYP3A4 inhibitors. Dose adjustment may be needed if other CNS-depressant drugs are used at the same time. Patients should be informed of the risks and should wait at least 12 hours before driving or engaging in other activities requiring full mental alertness.


Bupropion: serious cardiovascular events
Australia – The TGA is adding strengthened warnings to product information for bupropion (Zyban® and other brand names) as serious cardiovascular adverse events have been reported with this medicine in Australia. The events included myocardial infarction, cerebrovascular accidents, and severe hypertension requiring acute treatment. A higher rate of hypertension was observed when bupropion was combined with nicotine transdermal patches. Bupropion is registered for use in Australia as a short-term adjunctive therapy, in conjunction with counselling and abstinence, to assist in smoking cessation.

The TGA advises that care should be taken when using bupropion, especially in patients with a recent history of myocardial infarction or unstable heart disease as there is limited information about the safety of buproprion in these patients. Blood pressure should be monitored during treatment, especially in patients with pre-existing hypertension, and consideration be given to stopping treatment if a clinically significant increase is observed.

► Medicines Safety Update, Volume 5, Number 5, October 2014.

Galantamine hydrobromide: serious skin reactions
Canada – The manufacturer, in consultation with Health Canada, has provided new safety information
about the risk of serious skin reactions associated with the use of galantamine hydrobromide (Reminyl ER®), used for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer’s type. Very rare cases of serious skin reactions including cases of Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and erythema multiforme have been reported with this medicine. Health care professionals should inform patients and caregivers about the signs of these serious skin reactions, and discontinue the medicine at the first appearance of skin rash. (1)

Japan – The PMDA has requested a revision of the package insert for galantamine hydrobromide (Reminyl®), to include acute generalized exanthematous pustulosis in the section on clinically significant adverse reactions of the package insert. The change was based on expert opinions and available evidence from reports of this adverse event in other countries. (2)

Australia – the marketing authorization holder has updated the product information for Reminyl® and other galantamine-containing products to reflect the risk of serious skin reactions. (3)

► (1) Health Canada Advisory, 18 November 2014.
(2) PMDA Summary of investigation results: galantamine hydrobromide, 20 November 2014.
(3) TGA Safety advisory, 8 December 2014.

Dimethyl fumarate: rare brain infection
United States – The U.S. Food and Drug Administration (FDA) has alerted health professionals and the public that a patient with multiple sclerosis who was being treated with dimethyl fumarate (Tecfidera®) developed progressive multifocal leukoencephalopathy (PML), a rare and serious brain infection, and later died. The patient had taken dimethyl fumarate for more than four years before the adverse event occurred.

The FDA decided to add information describing this case on the drug label and has advised that patients taking dimethyl fumarate should contact their health care professionals right away if they experience symptoms such as new or worsening weakness; trouble using their arms or legs; or changes to their thinking, eyesight, strength or balance. Health care professionals should stop dimethyl fumarate if PML is suspected.


Omalizumab: slightly increased risk of heart and brain adverse events
United States of America – An FDA review of safety studies suggests a slightly higher risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the injectable asthma drug omalizumab (Xolair®) than in those who were not treated with the medicine. Information about these potential risks have been added to the drug label. Also, information about uncertain findings regarding a potential risk of cancer was added to the drug label.

Omalizumab is used to treat patients 12 years and older with moderate to severe persistent asthma and elevated immunoglobulin E levels, and those with chronic hives without a known cause, if these conditions cannot be controlled by other treatments. Health care professionals should periodically reassess
the need for continued therapy with omalizumab.
► [FDA Drug safety communication, 26 September 2014](http://www.fda.gov/Drugs/InformationOnDrugs/ucm382966.htm).

### Risk minimization measures

**Methylphenidate: web-based prescribing guide**

European Union – Following an EMA review of Ritalin® and other methylphenidate-containing medicines which called for the risk minimization measures (1), six MPH Marketing Authorisation Holders (MAHs) in the EU have collaborated in order to produce a web-based physician’s guide to methylphenidate prescribing (2).

Methylphenidate is part of a multi-modal treatment approach for attention deficit hyperactivity disorder (ADHD).

The website proposes checklists aiming to minimize the risk of cardiovascular, cerebrovascular, neuropsychiatric and growth disorders. Health professionals should review or complete these checklists before treatment starts and during therapy. The materials provided on the website should be used together with the full prescribing information for each individual product.


### Medicines review started

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| Dual anti-platelet therapy | Prevention of stent thrombosis and heart attacks | Preliminary clinical trial data have shown a higher overall risk of death with dual anti-platelet therapy for 30 months compared to 12 months. This risk was not observed in previous large trials. | ► [FDA, 16 November 2014](http://www.fda.gov/Drugs/InformationOnDrugs/ucm382966.htm).

### Site review started

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<tr>
<td>GVK Biosciences, Hyderabad, India</td>
<td>Contract research organization</td>
<td>Findings of non-compliance with good clinical practice. An inspection by the French medicines agency ANSM had raised concerns about study data used to support the marketing authorization applications of generic medicines. Some EU Member States have decided to suspend medicines marketing authorizations issued on the basis of studies conducted at the GVK Biosciences site.</td>
<td>EMA, 26 September 2014&lt;br&gt;WHO prequalification update, 7 August 2014&lt;br&gt;EMA Press release, 5 December 2014</td>
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### Manufacturing quality issues

#### Health Canada restricts imports from various Indian sites

Canada – Health Canada has taken action to restrict imports of finished pharmaceutical products from Apotex Research Private Limited, active pharmaceutical ingredients (APIs) from Apotex Pharmachem India Pvt Ltd and from IPCA Laboratories, as well as products made with APIs from these sites (1). Health Canada has also restricted the import of health products from three Micro Labs facilities in India: Bangalore, Goa and Hosur (2). Only products that are on authority’s “medically necessary” list will be allowed on the market, subject to prior testing by an independent third party.

In both cases, the regulatory action was triggered by data integrity concerns identified in inspections by international partners. The import ban is a precautionary measure. No specific safety issues have been identified with products already on the market, and neither Health Canada nor its regulatory partners have requested a recall of these products. Health Canada continues to work with regulatory partners to monitor compliance with good manufacturing practices at the sites.

World Health Organization – In June 2014 the WHO Prequalification Team had published on its website a notice of concern addressed to Micro Labs Ltd (3). To date the notice of concern has not been lifted. In August 2014 the prequalification team published information about WHO action taken regarding the deficiencies noted at the IPCA site (4).