Safety news

Restrictions

Metoclopramide: not for children under one year of age
Canada – The marketing authorization holder, in consultation with Health Canada, has warned that neurological adverse events can occur in children receiving metoclopramide within the daily recommended dosage of 0.5 mg/kg. Metoclopramide is now contraindicated in children less than one year of age in Canada, as a Health Canada review has shown that they are at greater risk of abnormal involuntary movements (extrapyramidal symptoms). In children over one year metoclopramide should only be used if the anticipated benefits clearly outweigh the potential risks.

► Health Canada Advisory, 5 January 2015.

Domperidone: further restrictions
United Kingdom – Further to a recommendation by the European Medicines Agency (EMA) to restrict the use of domperidone to the management of nausea and vomiting due to adverse effects on the heart (see WHO Drug Information Vol. 28, No. 2), domperidone-containing medicines have been restricted in the United Kingdom for supply on prescription only with effect from 4 September 2014. (1)

New Zealand – A Medsafe review has concluded that domperidone-containing medicines have a small increased risk of adverse heart effects, which may be higher in patients over 60 years or at total daily doses of more than 30 mg. The manufacturer has decided to reduce the maximum recommended dose from 80 mg to 40 mg daily. (2)

Canada – Health professionals have been informed of additional safety information about some cardiac risks associated with domperidone. The medicine is now contraindicated in Canada in patients with prolonged of cardiac conduction intervals, significant electrolyte disturbances, cardiac disease or liver impairment, and those receiving QT-prolonging drugs or potent CYP3A4 inhibitors. Domperidone should be used at the lowest effective dose up to a maximum recommended daily dose of 30 mg and for the shortest possible duration.

► (1) Drug Safety Update volume 8 issue 2, September 2014: S1.
► (2) Medsafe Safety information, 22 December 2014.

Nitrofurantoine: revised contraindication in renal impairment
United Kingdom – The Medicines and Healthcare Products Regulatory Agency (MHRA) has recommended to lower the estimated glomerular filtration rate (eGFR) below which nitrofurantoin is contraindicated. Its use should now be allowed in patients with an eGFR of 45 ml/min/1.73m² or more (previously: 60 ml/min/1.73m²). A short course (3 to 7 days) may be used with caution in certain patients with an eGFR of 30–44 ml/
min/1.73m² to treat lower urinary tract infection with suspected or proven multidrug-resistant pathogens.

The efficacy of nitrofurantoin in treating and preventing urinary tract infections depends on its renal secretion into the urinary tract. The revised recommendations consider the fact that lower urinary tract pathogens are increasingly resistant to standard therapy (trimethoprim and amoxicillin), and that the widespread use of alternative broad-spectrum antibiotics (cephalosporins and fluoroquinolones) is associated with the risk of *Clostridium difficile* colitis.


### Oral diclofenac: prescription-only in United Kingdom

**United Kingdom** – Diclofenac 12.5mg and 25mg tablets, formerly available over the counter, have been re-classified as a prescription-only medicine in the United Kingdom with effect from 15 January 2015.

A 2013 Europe-wide review had found that systemic diclofenac is associated with a small increased risk of arterial thromboembolic events, similar to that of COX-2 inhibitors. In the United Kingdom the Commission on Human Medicines (CHM) has reconsidered available evidence and has concluded that the risk of these side effects cannot be ruled out even when the medicine is taken for a short time or at a lower dose. The Commission therefore advised that patients should have a medical review before taking oral diclofenac to make sure it is suitable for them.


### Risperidone: not to be used in vascular or mixed-type dementia

**Canada** – Health Canada has restricted the indication for risperidone (Risperdal®) in dementia to the short-term symptomatic management of aggression or psychotic symptoms in patients with severe dementia of the Alzheimer type unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. The indication no longer includes the treatment of other types of dementia.

The recommendation is based on available safety information on antipsychotic drugs, indicating a higher risk of cerebrovascular adverse events in patients with mixed and vascular dementia compared to those with dementia of the Alzheimer type.


### Hydroxyzine: new restrictions

**European Union** – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review of medicines containing the antihistamine hydroxyzine. These are available in most EU countries for various indications such as treatment of anxiety disorders and sleep disorders, relief of itching caused by urticaria, and as premedication before surgery.

The PRAC considered that hydroxyzine is associated with a small but definite risk of QT interval prolongation and torsade de pointes, which can lead to abnormal heart rhythms and cardiac arrest.

To minimize the risk the Committee has recommended a number of restrictions. Use is not recommended in the elderly. Duration and dosage should be reduced to minimum effective levels. The maximum daily dose should be no more than 100 mg
in adults (50 mg in the elderly if use cannot be avoided), and 2 mg per kg body weight in children up to 40 kg in weight. Use must be avoided in patients who have risk factors for arrhythmias or are taking other medicines associated with QT prolongation; care is needed in patients taking medicines that slow the heart rate or decrease blood potassium levels.


**Codeine-containing cough and cold medicines: not for children under 12**

New Zealand – Medsafe’s Medicines Adverse Reactions Committee has recommended to restrict the use of all codeine-containing cough and cold medicines for children, including prescription-only-medicines, to children aged 12 years and over. An EMA review of these medicines started in April 2014 following concerns of morphine toxicity and respiratory depression.

► Minutes of the 160th Medicines Adverse Reactions Committee Meeting, 4 December 2014.

**Safety warnings**

**Linagliptin: possible liver toxicity**

Japan – Following reports of hepatic dysfunction in patients treated with linagliptin in Japan, the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan have recommended to update the product information to include this risk.

Health professionals should monitor patients treated with linagliptin for signs of liver dysfunction, including liver enzyme elevations, and should consider stopping linagliptin in case of abnormalities.

► PMDA Summary of investigation results and Revisions of Precautions for linagliptin, 9 January 2015.


**Apixaban: interstitial lung disease**

Japan – The MHLW/PMDA has recommended to revise the product information for the anti-coagulant apixaban (Eliquis®) following reported cases of haemorrhage and bloody sputum suggestive of interstitial lung disease, including suspected interstitial pneumonia in some cases.

► PMDA Summary of investigation results, 17 February 2015.

**Chlorhexidine: chemical burns in premature infants**

United Kingdom – The MHRA has warned health professionals that alcohol-based and aqueous chlorhexidine solutions used for skin antisepsis prior to invasive procedures can cause chemical burns in neonates. This risk appears to be higher in preterm infants, especially those born before 32 weeks of gestation, and within the first two weeks of life.

Health professionals should remove any soaked materials before proceeding with the intervention. They should not use excessive quantities of chlorhexidine and should not allow the solution to pool in skin folds or under the patient or to drip on any material in direct contact with the patient. Before applying occlusive dressings, care must be taken to remove any excess chlorhexidine.

Testosterone: caution about use in healthy men
United States of America – The U.S. FDA has cautioned about using testosterone products to treat low testosterone levels due to aging. The Agency requires labelling changes to clarify the approved indications of testosterone and to inform health professionals and patients of possible increased risks of heart attack and stroke associated with the use of these products.

Prescription testosterone products are approved in the U.S. only to treat low testosterone levels caused by certain medical conditions. The FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone levels for no apparent reason other than aging. The Agency cautions that the benefit and safety of these medications have not been established in this patient group – even if a man’s symptoms seem related to low testosterone – and that some studies in aging men treated with testosterone have reported an increased risk of heart attack, stroke or death. (1)

Warnings about the possible cardiac risks associated with testosterone have also been communicated recently by the EMA and New Zealand's Medsafe (2).

Telaprevir: renal impairment
Japan – The MHLW/PMDA has recommended a revision of the product information for telaprevir, used to treat chronic hepatitis C infection, advising health professionals to consider a reduced initial dose in patients who are at risk of renal impairment.

The recommendation is based on an interim analysis of post-marketing surveillance survey data indicating that a full initial dose, higher age, increased baseline creatinine, and diabetes mellitus or hypertension as comorbidities are risk factors for serious renal impairment in patients treated with telaprevir.

► PMDA Summary of investigation results, 17 February 2015.

Simeprevir: leukopenia and neutropenia
Japan – Following reports of adverse events suggestive of leukopenia and/or neutropenia in patients treated with combination therapy of simeprevir sodium, peginterferon and ribavirin in Japan, the MHLW/PMDA has recommended to revise the package insert for simeprevir. Health professionals should monitor patients for leukopenia and/or neutropenia, and should consider stopping simeprevir in case of severe abnormalities.

► PMDA Summary of investigation results and Revision of Precautions for simeprevir sodium, 9 January 2015.

Mycophenolate mofetil and mycophenolic acid: hypogammaglobulinaemia and bronchiectasis
United Kingdom – In accordance with a review and recommendations by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC), the marketing authorization holder of mycophenolate mofetil (CellCept®) in the United Kingdom has informed health professionals of the risk of hypogammaglobulinaemia and the
risk of bronchiectasis associated with the medicine. Mycophenolate mofetil is registered in the United Kingdom to prevent acute transplant rejection and is used off-label in a number of specialties.

Serum immunoglobulin levels should be measured in patients developing recurrent infections and clinical action taken as needed, taking into account the potent cytostatic effects of the drug on B- and T-lymphocytes. In case of persistent respiratory symptoms bronchiectasis or pulmonary fibrosis should be suspected.

► Drug Safety Update volume 8 issue 6, January 2014: 3.

Vemurafenib: pancreatitis

Canada – A new warning about the risk of pancreatitis has been added to the Canadian prescribing information for vemurafenib (Zelboraf®). Vemurafenib is used to treat unresectable or metastatic melanoma with a BRAF mutation in adult patients.

Cases of drug-induced pancreatitis have been reported with the use of vemurafenib both in Canada and elsewhere. The reactions generally occurred during the first two weeks of treatment. Health professionals should suspect pancreatitis in patients taking vemurafenib and presenting with unexplained abdominal pain. If vemurafenib is re-started after an episode of pancreatitis, patients should be closely monitored and a dose modification should be considered.

► Health Canada Advisory, 12 February 2015.

Ziprasidone: rare but potentially fatal skin reactions

United States of America – The FDA has warned that the antipsychotic drug ziprasidone (Geodon® and generics) is associated with a rare but serious skin reaction known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which can progress to affect other parts of the body and can be fatal.

A warning about this risk has been added to the label of the capsule, oral suspension and injection formulations of this drug. Patients who have a fever with a rash and/or swollen lymph nodes should seek urgent medical care. Health care professionals should immediately stop treatment with ziprasidone if DRESS is suspected.

► FDA Drug safety communication, 11 December 2014.

Abiraterone: thrombocytopenia

Japan – The MHLW/PMDA has recommended to revise the product information for abiraterone tablets (Zytiga®), used to treat castration-resistant prostate cancer, to warn health professionals of the risk of thrombocytopenia (1). A safety signal was identified in 2013 from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase™, warranting further investigation (2).

The product information in Japan was updated at the same time to include the risks of hypokalaemia and rhabdomyolysis, two adverse events already reflected in FDA- and EMA-approved product information.

► (1) PMDA Revisions of precautions, 2 February 2015.

Donepezil: rhabdomyolysis and neuroleptic malignant syndrome

Canada – Health Canada has communicated new warnings for donepezil, used in the treatment of Alzheimer’s disease. This medicine is associated with a risk of two rare but potentially serious conditions: rhabdomyolysis, a rare condition involving the breakdown of muscle tissue, and neuroleptic malignant syndrome (NMS), a very rare life-threatening disorder characterized by a chemical imbalance that affects the nervous, muscular and cardiovascular systems.

Before prescribing donepezil health professionals should assess patients for risk factors for rhabdomyolysis such as: muscular disorders, uncontrolled hypothyroidism, liver or kidney damage, and concomitant use of other medicines that can cause rhabdomyolysis such as statins, antipsychotics, and certain types of antidepressants. Donepezil therapy should be stopped if blood tests show high levels of creatine phosphokinase (CPK), and/or if NMS and/or rhabdomyolysis is diagnosed.

► Health Canada Advisory, 21 January 2015.

Ambroxol/bromhexine: rare severe skin reactions

European Union – The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) – a regulatory body representing EU Member States – has endorsed recommendations to add information about a small risk of severe allergic reactions, including severe cutaneous adverse reactions (SCARs) such as erythema multiforme and Stevens-Johnson syndrome, to the product information for ambroxol- and bromhexine-containing medicines, which are widely used in the EU as expectorants.

The recommendations originated from the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC), whose review of the two medicines confirmed the known risk of allergic reactions and identified a small risk of SCARs.


Nitric oxide cylinders: faulty valves

European Union – The manufacturer, in cooperation with EMA and national regulatory authorities, has informed health professionals in EU Member States that a defect might cause the valves in some nitric oxide (INOmax®) cylinders to close while in use and before the cylinder is emptied. This abruptly stops gas delivery earlier than expected. Life-threatening rebound effects can occur if the cylinder is not changed immediately.

The defect applies to 400 ppm and 800 ppm cylinders of both the 2 L and 10 L pack sizes. To minimize the adverse reactions health professionals should always have a full spare cylinder loaded onto the delivery device, always use devices with pressure sensor monitors and gas monitor alarms, and when switching cylinders purge the regulator of the second cylinder before connecting it to the device to prevent excessive NO₂ formation. For all patient transfers, even short transfers, back-up cylinders should be kept available.

Unchanged recommendations

Analgesics in pregnancy
United States of America – In response to reports questioning the safety of pain medicines during pregnancy, the FDA has reviewed three types of potential risks: 1) risk of miscarriage following use of prescription non-steroidal anti-inflammatory drugs (NSAIDs) in the first half of pregnancy, 2) risk of birth defects following administration of opioids during the first trimester of pregnancy, and 3) risk of attention deficit hyperactivity disorder in the infant following paracetamol use at any time of pregnancy.

The studies reviewed did not provide sufficiently consistent data to allow reliable conclusions. FDA recommendations on the use of analgesics during pregnancy will remain unchanged.

► FDA Drug safety communication, 9 January 2015.

Manufacturing quality issues

GVK Biosciences: EMA recommends suspensions
European Union – The EMA’s Committee for Medicinal Products for Human Use (CHMP) has recommended to suspend some 700 pharmaceutical forms and strengths of medicines authorized in EU Member States based primarily on clinical studies conducted at GVK Biosciences in Hyderabad, India.

An inspection by the French medicines agency ANSM had raised concerns about prolonged and systematic non-compliance with good clinical practice at GVK’s Hyderabad site. This does not mean that the medicines concerned are necessarily unsafe for patients, but that reliable data are needed to prove their bioequivalence.

The CHMP has identified those medicines for which insufficient clinical data are available from other sites, and has recommended their suspension unless a national authority considers that a medicine is of critical importance to meet patients’ needs in the specific EU Member State. In that case, the marketing authorization holder is given 12 months to submit additional data. (1)

Some marketing authorisation holders have requested a re-examination. (2)

Switzerland – The Swiss Agency for Therapeutic Products (Swissmedic) has identified three products that are authorized for export from Switzerland on the basis of clinical trials by GVK Biosciences in Hyderabad (India). Swissmedic will now review these authorizations in detail. (3)

WHO – Two products prequalified by WHO for purchase by UN agencies have been withdrawn voluntarily by the company from the WHO prequalification list; new data are under assessment for a third prequalified product. (4)

► (1) EMA Press release, 23 January 2015.
(2) EMA News, 27 February 2015.
(3) Swissmedic Announcement, 6 February 2015.
(4) PQP Information note, 16 January 2015.

Three Indian sites: Canada stops imports
Canada – Health Canada has requested Canadian importers to stop the importation and distribution of products from a number of manufacturing sites in India due to data integrity concerns. Action taken in December 2014 applied to active
pharmaceutical ingredients (APIs) from Dr. Reddy’s Laboratories in Srikakulam and to finished drug products from IPCA Laboratories in Pithampur; action taken in January 2015 applied to health products made with APIs from Sri Krishna Pharmaceuticals Ltd. in Hyderabad, India.

In September and October 2014 Health Canada had already imposed import restrictions on pharmaceutical products from some Indian sites, including another IPCA Laboratories facility (see WHO Drug Information, Vol. 28, No. 4).

The import stop is a precautionary measure. Health Canada has not identified a risk to health, nor has it requested a recall of any of the products.

► Health Canada Advisory, 6 January 2015.

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**Falsified product alert**

**Falsified artemether/lumefantrine in West Africa**

Following notification from the Global Fund to Fight AIDS, Tuberculosis and Malaria, WHO has received confirmation that falsified packs of artemether/lumefantrine antimalarial tablets have been found in West Africa. The falsified products contain none of the correct active pharmaceutical ingredients. The packs bear the following markings:

- **Falsified product purchased in a street market in Abidjan, Côte d’Ivoire:**
  - Batch number: DYI402542 on the box (secondary packaging)
  - DYI402201 on the blister foil (primary packaging)
  - Manufacturing date: 07/2013, Expiry date: 06/2016

- **Falsified product found in a drug store in Lomé, Togo during an INTERPOL operation:**
  - Batch number: DYI402541 on the outer bulk pack (tertiary packaging)
  - DYI402542 on the box (secondary packaging)
  - DYI402201 on the blister foil (primary packaging)
  - Manufacturing date: 07/2013, Expiry date: 07/2016

All the above packaging levels bear the ACTm green leaf logo of the Affordable Medicines Facility malaria programme. The writing on the packaging is in English.

WHO is calling for increased vigilance for these specific batches of this product. To report any information concerning these batches, or to report other incidents concerning falsified medicines, please contact rapidalert@who.int.

► WHO Medical Product Alert No. 1/2015, February 2015. (Includes photographs)