Safety and efficacy news

Substandard and falsified products

Falsified antimalarial medicines in West and Central Africa
World Health Organization – WHO warns about three separate falsified antimalarial medicines discovered in Cameroon, Ghana and Liberia. The medicines concerned are falsely labelled as Rivopharm Laboratories Sulfadoxine/Pyrimethamine BP 500mg + 25mg, Biochemie GmnH Quinine Sulphate 300mg B.P. and Weiders Farmasotiske Quinine Sulphate 300mg USP. They are circulating in packs of 1000 tablets with English and French labelling containing spelling mistakes and bearing a previous WHO Essential Drugs Programme logo, which is no longer in use by WHO.

National regulatory authorities are requested to increase vigilance within the formal and informal supply chains for these products as described in more detail in the WHO Drug Alert. If any other medicines are discovered bearing the discontinued WHO Essential Drugs Programme logo, steps should be taken to ensure that they meet full specifications.

Falsified antimalarial medicines in West and Central Africa

Stolen trastuzumab, pemetrexed and infliximab in Europe
European Union – The European Medicines Agency (EMA) has informed the public about the theft of trastuzumab, pemetrexed and infliximab vials in Italy, some of which were later reintroduced illegally into the supply chain in other countries. There is evidence that some of the trastuzumab vials had been tampered with. National health and law enforcement authorities are working to identify all concerned batches and take appropriate measures to protect the health of EU citizens.

EMA warned that the products with the batch numbers listed in the EMA press release must not be used because they cannot be considered safe or effective. Health professionals were advised to be alert when handling any other batches of the concerned medicines, and to report any suspicion of authenticity immediately to the local health authorities.

Stolen trastuzumab, pemetrexed and infliximab in Europe
EMA Press releases, 16 April 2014 and 17 April 2014.

Safety information

Diacerein-containing medicines: restricted use
European Union – The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) of the European Medicines Agency (EMA) has endorsed recommendations to restrict the use of diacerein-containing medicines in order to manage the risks of severe diarrhoea and effects on the liver. Diacerein-containing medicines are currently authorized in the following EU Member States: Austria, Czech Republic, France, Greece, Italy, Portugal, Slovakia and Spain.

Diacerein should only be used to treat osteoarthritis affecting the hip or knee in patients aged under 65 years who do not have current or past liver disease. Treatment should be initiated by an experienced health care professional.
Treatment should start at half the normal dose for the first 2-4 weeks and should be stopped if diarrhoea or signs of liver problems occur.

**Domperidone: adverse effects on the heart**

**European Union** – The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has completed its review of domperidone, triggered by concerns expressed by the Belgian medicines authority about the medicine’s effects on the heart.

The Committee recommended using domperidone only to manage nausea and vomiting – not other conditions such as bloating or heartburn – and reducing the dose in adults to 10 mg up to three times daily by mouth or 30 mg twice daily as suppositories. Where the medicine is licensed in children weighing less than 35 kg it should be given orally at a dose of 0.25 mg per kg bodyweight up to three times daily. The medicine should not normally be used for longer than one week.
► EMA News, 7 March 2014.
(See also under “Reviews started”)

**Hydroxyethyl starch-containing products: increased risk for patients with sepsis**

**Australia** – The Therapeutic Goods Administration (TGA) advises the public that a recent safety review of hydroxyethyl starch-containing products (Voluven® and Volulyte®) has confirmed an increased risk of mortality and the need for dialysis when this medicine is used to treat patients with sepsis. Hydroxyethyl starch-containing solutions are administered in clinical situations, including during surgery, to treat and prevent hypovolaemia.

In 2013 the product information was updated to include new contraindications for patients with sepsis and patients with severe liver disease, as well as changes to the precautions and dosage and administration sections. The safety review has found that the updates are sufficient to mitigate the risks.
► TGA Safety Advisory, 4 April 2014.

**Epidural corticosteroid injection: rare but serious neurologic problems**

**United States of America** – The U.S. Food and Drug Administration (FDA) is requiring a warning on drug labels that epidural injection of corticosteroids may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death.

Injectable corticosteroids include methylprednisolone, hydrocortisone, triamcinolone, betamethasone, and dexamethasone. This safety issue is unrelated to the contamination of compounded corticosteroid injection products reported in 2012.

Epidural injection of corticosteroids to relieve neck and back pain has been a widespread practice for many decades; however, the FDA has not approved corticosteroids for such use. A panel of experts is working to define the techniques for such injections which would reduce preventable harm. The FDA will continue to investigate this issue.
► FDA Safety Announcement, 23 April 2014.

**Zolpidem, eszopiclone: impaired next-day alertness**

**European Union** – The European Medicines Agency (EMA)’s Coordination Group for Mutual Recognition and Decentralised Procedures – Human
(CMDh) has endorsed new advice to minimize the risk of next-morning impaired driving ability and mental alertness associated with the sleeping medication zolpidem.

The product information of zolpidem-containing medicines will be updated to include strengthened warnings and precautions. The recommended doses must not be exceeded. Patients should take the lowest effective dose of zolpidem in a single intake, should not take any alcohol, illicit drugs or medicines affecting the central nervous system together with zolpidem, and should not drive or perform activities that require mental alertness for at least 8 hours after taking zolpidem.


United States of America – The U.S. Food and Drug Administration (FDA) warns that eszopiclone – similar in structure to zolpidem – is associated with next-day impairment of alertness, often not noticed by the patient. Eszopiclone-containing medicines marketed in the United States include Lunesta® and generics. The recommended starting dose was reduced from 3 mg to 1 mg at bedtime. Higher doses can be taken if needed, but are more likely to impair next-day alertness. Patients should not drive or engage in other activities that require mental alertness on the day after taking a 3 mg dose. Product information was updated to include these changes.

► FDA Safety announcement, 15 May 2014.

Mirtazapine: abnormal heart rhythm
Canada – Merck Canada Inc., in consultation with Health Canada, has informed health professionals of post-marketing cases of QT prolongation and torsades de pointes reported with the use of the antidepressant mirtazapine (Remeron® / Remeron RD®). Most cases occurred in association with drug overdose or in patients with preexisting risk factors for QT prolongation. Serious outcomes including torsades de pointes and death have been reported with mirtazapine overdose.

Mirtazapine should be used with caution in patients with known cardiovascular disease, a family history of QT prolongation or concomitant use of QT prolonging medications. Vital signs and cardiac rhythm should be monitored in case of a mirtazapine overdose.

► Health Canada Advisory, 28 March 2014.

Vemurafenib: liver problems
Canada – Hoffmann-La Roche Limited (Roche Canada) and Health Canada have informed health professionals of cases of drug-induced liver injury, some of them severe, reported with vemurafenib (Zelboraf®). Vemurafenib is indicated for the treatment of certain types of unresectable or metastatic melanoma. Health professionals should monitor patients’ liver enzymes and bilirubin before and during treatment. Liver problems should be managed by reducing the dose of vemurafenib, or by interrupting or stopping the treatment.

► Health Canada Advisory, 7 April 2014.

Filgrastim and pegfilgrastim: capillary leak syndrome
Canada – Health Canada in association with the manufacturer has warned about the risk of capillary leak syndrome associated with filgrastim and pegfilgrastim, two medicines used to treat neutropenia. Capillary leak syndrome has been reported in cancer patients undergoing chemotherapy who were...
treated with either of the medicines, and in bone marrow donors undergoing peripheral blood progenitor cell mobilization who were receiving filgrastim.

Capillary leak syndrome, the leaking of fluid from the circulatory system into the interstitial space, can cause circulatory shock and may be fatal. In case of suspected symptoms – such as swelling or puffiness, passing water less frequently, difficulty breathing, and tiredness – treatment must be stopped and the patient closely monitored.

► Health Canada Advisory, 10 April 2014.

Belimumab: opportunistic brain infection
Canada – Health Canada in association with the manufacturer has warned health professionals about two cases of progressive multifocal leukoencephalopathy (PML), an opportunistic brain infection, reported in patients receiving belimumab (Benlysta®) for systemic lupus erythematosus.

Health professionals should suspect PML in patients with new onset deficits or deterioration in cognition, speech or eye functions, seizures and/or motor and gait disturbances. A neurologist should be consulted urgently, and where appropriate immunosuppressants including belimumab should be withheld until PML is excluded.

► Health Canada Advisory, 22 April 2014.

Temozolomide: liver injury
Canada – Health Canada in association with the manufacturer has warned health professionals about cases of liver injury, including fatal liver failure, reported in patients taking temozolomide (Temodal®) for the treatment of glioblastoma. Liver toxicity may occur several weeks after initiation of treatment or after temozolomide discontinuation. Liver function should be tested before and during treatment. In case of significant abnormalities, the benefits and risks of continuing treatment should be carefully considered.

► Health Canada Advisory, 7 May 2014.

RAS-acting agents: not to be used in combination
European Union – The European Medicines Agency (EMA)’s Pharmacovigilance Risk Assessment Committee (PRAC) has advised against the combined use of two medicines of different classes acting on the renin-angiotensin (RAS) system. RAS-acting agents are used in the treatment of hypertension and congestive heart failure and include three main classes: angiotensin-receptor blockers (ARBs or “sartans”), angiotensin-converting enzyme inhibitors (ACE-inhibitors) and direct renin inhibitors such as aliskiren.

In particular, patients with diabetes-related kidney problems should not be given an ARB with an ACE-inhibitor; where this is absolutely necessary treatment must be supervised by a specialist with close monitoring of kidney function, fluid and salt balance and blood pressure. The combination of aliskiren with an ARB or ACE-inhibitor is strictly contraindicated in those with kidney impairment or diabetes. This confirms and strengthens the conclusions of a 2012 EMA review of aliskiren.

► EMA News, 11 April 2014.

TNF-alpha inhibitors: reactivation of tuberculosis
United Kingdom – The U.K. Medicines and Healthcare products Regulatory Agency (MHRA) has warned about an increased risk of tuberculosis, or
reactivation of latent tuberculosis, during treatment with tumour necrosis factor alpha (TNF-alpha) inhibitors.

Tuberculosis in patients receiving TNF-alpha inhibitors can be life-threatening, and deaths from tuberculosis have occurred in these patients. TNF-alpha inhibitors are therefore contraindicated in patients with active tuberculosis or other severe infections.

Patients should be screened for active and latent tuberculosis before starting treatment with a TNF-alpha inhibitor, and should be monitored closely for tuberculosis and other infectious diseases before, during, and after treatment.

► MHRA Drug Safety Update 7(9); April 2014.

**Arsenic-containing dental pastes: genotoxicity**

European Union – The European Medicines Agency (EMA)’s Committee for Medicinal Products for Human Use (CHMP) has recommended that the marketing authorizations for the dental pastes containing arsenic trioxide (Caustinerf arsenical®, Yranicid arsenical® and associated names) be revoked in the EU due to concerns over genotoxic effects that could increase the risk of cancer, and the risk of cell death if the product leaks into tissues around the teeth.

The dental pastes have been used to remove damaged nerves in the dental pulp. The CHMP considered that restrictions and additional guidance to dentists would not reduce the risks to an acceptable level.


**Serotonin-blocking medicines: serotonin syndrome**

Canada – Health Canada has completed a safety review of the serotonin-blocking drugs dolasetron (Anzemet®), granisetron (Kytril® and generics), ondansetron (Zofran® and generics) and palonosetron (Aloxi®), which are used for treating nausea and vomiting. This review identified a potential risk of serotonin syndrome, caused by serotonin accumulation in the body.

Early diagnosis is vital as serotonin syndrome can be fatal if not treated. Symptoms may include agitation, confusion, fast heartbeat, muscle twitching or stiffness, fever, loss of consciousness or coma.

The product monographs for the affected serotonin-blocking products on the Canadian market are being updated to include this new safety information.

► Health Canada Advisory, 14 May 2014.

**Panitumumab: rare but severe skin reactions**

Canada – Health Canada and the manufacturer has informed health professionals of rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis reported in patients treated with panitumumab (Vectibix®), approved for the treatment of certain types of metastatic colorectal cancer. The product monograph is being updated accordingly.

► Health Canada Advisory, 27 May 2014.
## Overview of safety reviews started

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Uses</th>
<th>Concerns</th>
<th>Reviewing authority reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>Treatment of relapsing-remitting multiple sclerosis</td>
<td>Melanoma</td>
<td><img src="#" alt="TGA Monitoring communication, 18 March 2014" /></td>
</tr>
<tr>
<td>Domperidone</td>
<td>Relief of symptoms of nausea and vomiting, and delayed stomach emptying</td>
<td>Adverse effects on the heart</td>
<td><img src="#" alt="TGA Monitoring communication, 2 April 2014" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="#" alt="Medsafe Monitoring communication, 31 March 2014" /></td>
</tr>
<tr>
<td>Oral methadone medicines containing povidone</td>
<td>Relief of withdrawal symptoms in patients dependent on opioids</td>
<td>Kidney failure possibly linked to misuse</td>
<td><img src="#" alt="EMA Press release, 11 April 2014" /></td>
</tr>
<tr>
<td>Codeine-containing medicines</td>
<td>Cough and cold in children</td>
<td>Morphone toxicity</td>
<td><img src="#" alt="EMA Press release, 11 April 2014" /></td>
</tr>
<tr>
<td>Testosterone-containing medicines</td>
<td>Treatment of hypogonadism</td>
<td>Heart problems</td>
<td><img src="#" alt="EMA Press release, 11 April 2014" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="#" alt="EMA Press release, 11 April 2014" />  (See also FDA Safety announcement, 31 January 2014)</td>
</tr>
<tr>
<td>Ambroxol and bromhexine</td>
<td>Expectorants; treatment of breathing disorders in newborns</td>
<td>Allergic reactions and severe skin reactions</td>
<td><img src="#" alt="EMA Press release, 11 April 2014" /></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Treatment of symptoms in adults with long-term stable angina or long-term heart failure</td>
<td>Increased combined risk of cardiovascular death or non-fatal heart attack in patients with symptomatic angina</td>
<td><img src="#" alt="EMA Press release, 8 May 2014" /></td>
</tr>
<tr>
<td>Hydroxyzine-containing medicines</td>
<td>Various, including treatment of anxiety disorders, sleep disorders premedication before surgery, relief of itching</td>
<td>Adverse effects on the heart</td>
<td><img src="#" alt="EMA Press release, 8 May 2014" /></td>
</tr>
</tbody>
</table>