Safety and Efficacy Issues

Contaminated dextromethorphan

World Health Organization — On 24 January 2013, a WHO Drug Alert was issued following the discovery in Pakistan of two types of locally produced cough syrup containing the contaminated active pharmaceutical ingredient (API) dextromethorphan.

This incident led to the death of approximately 50 persons in Pakistan, all with a history of drug addiction, who had been abusing dextromethorphan-containing syrup for many years without any reported unexpected adverse reactions. The subsequent investigation found that manufacturers in Pakistan were obtaining the dextromethorphan API from a source in India.

Full laboratory testing of the dextromethorphan showed that it was contaminated with levomethorphan, the enantiomer of dextromethorphan, which is a potent opioid analgesic internationally controlled under Schedule 1 of the Single Convention on Narcotic Drugs (1961).

In January 2013, as a result of this incident, the Indian regulatory authorities suspended the manufacture, distribution, sale or use of the dextromethorphan in question.

WHO called on all countries to increase vigilance concerning dextromethorphan in general and to ensure that the API met all required quality specifications.

On 26 September 2013, WHO was notified of suspected drug intoxication involving eleven paediatric patients in Paraguay. All of the patients were experiencing influenza-like symptoms and had consumed medical products produced by a local manufacturer containing dextromethorphan. The children were aged from 2–9 years and serious adverse reactions included altered consciousness, cyanosis, respiratory distress and seizures. Onset of symptoms occurred from 2–7 hours after ingesting dextromethorphan. Since then, the number of patients experiencing adverse reactions rose to 44 confirmed cases, ranging in age from 5 months to 48 years. There was one fatality that may be linked to the event.

The Paraguayan Ministry of Health issued warnings concerning the medicines thought to be connected to this incident. Investigations by the Paraguayan authorities subsequently indicated the source of the API dextromethorphan to be the same Laboratories in India. The batch number of the dextromethorphan API used by the Paraguayan manufacturer was the same as one of the contaminated batches found in Pakistan. However, the Paraguayan manufacturer appears to have ordered the API in 2012, prior to events in Pakistan.

According to the local manufacturer in Paraguay none of the products have been exported, however they could possibly be available in neighbouring countries through local traders and travellers.

WHO advises extra vigilance for the API dextromethorphan and strongly urges that extreme caution be exercised by importing countries and manufacturers. Dextromethorphan should be carefully tested for the presence of the contaminant levomethorphan, and it should meet the recognized specifications.
Samples of contaminated dextromethorphan API from the original Pakistan incident have been analysed at the request of WHO and revealed limits of levomethorphan varying between 9.5% to 22.6%. All of the samples tested in both incidents have failed to comply with the requirements for the specific optical rotation as specified in the monograph for dextromethorphan hydrobromide published in The International Pharmacopeia.


Falsified artemether and lumefantrine circulating in Cameroon

World Health Organization — A WHO Drug Alert has been circulated concerning falsified batches of Coartem® that are circulating in Western and Central Africa. Coartem® is a fixed-dose artemesinin based combination therapy (ACT) (artemether 20 mg and lumefantrine 120 mg) used for the treatment of Plasmodium falciparum malaria. The genuine product is manufactured by Novartis and is a WHO prequalified medicine.

On 5 November 2013, Novartis informed WHO of further falsified versions of Coartem® recently circulating in Cameroon as follows:

- Batch Number: NOF 2153
  Manufacturing Date: 01.2013
  Expiry Date: 11.2015

- Batch Number F2929
  Manufacturing Date: 01.2012
  Expiry Date: 01.2016

The packaging of both batches is in English and bears the falsified green leaf logo of the Global Fund Affordable Medicines Facility – Malaria (AMFm) Programme.

Details of falsified batches of Coartem® circulated by WHO in May 2013 are as follows:

- Batch number: F1901
  Manufacturing Date: 01.2012
  Expiry Date: 01.2014

The packaging is in English and bears a falsified stamp of the Nigerian National Medicines Regulatory Agency, NAFDAC.

- Batch Number: F2261
  Manufacturing Date: 01.2012
  Expiry Date: 01.2014

The packaging is in English and bears the falsified green leaf logo of the Affordable Medicines Facility – Malaria (AMFm) Programme. Novartis has informed WHO that this batch has also been seen again recently in Cameroon.

All four batches are packaged for adult use and distribution within the public sector. The falsified batches contain little or no active pharmaceutical ingredient and are therefore ineffective.

Some of these batches have been found in a number of West and Central African countries in hospitals and street markets. Increased vigilance throughout the region is strongly advised. Hospitals, clinics, and pharmacies should check their stocks for these batches and report any suspicions to their national medicines regulatory authority.


Ponatinib: increased reports of serious blood clots

United States of America — The Food and Drug Administration (FDA) is investigating the increased frequency of reports of serious and life-threatening blood clots and severe narrowing of
Intravenous tigecycline: increased risk of death

United States of America — The Food and Drug Administration (FDA) is warning that an additional analysis shows an increased risk of death when intravenous tigecycline (Tygacil®) is used for approved or non-approved uses. Healthcare professionals should reserve tigecycline for use in situations when alternative treatments are not suitable. Tigecycline is approved to treat complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia. Tigecycline is not indicated for treatment of diabetic foot infection or for hospital-acquired or ventilator-associated pneumonia.

In 2010, FDA informed the public that a meta-analysis of 13 Phase III and IV trials showed a higher risk of death among patients receiving Tygacil® compared to other antibacterial drugs. The increased risk was greatest in patients treated for ventilator-associated pneumonia, a use for which FDA has not approved the drug.

Since 2010, FDA has analysed data from ten clinical trials conducted only for FDA-approved uses showed a higher risk of death among patients receiving Tygacil® compared to other antibacterials. In general, the deaths resulted from worsening infections, complications of infection, or other underlying conditions.


Cinacalcet: hypocalcaemia and arrhythmia

Canada — A safety review of the drug cinacalcet (Sensipar®) has identified a possible link to arrhythmia associated with low blood calcium. Cinacalcet is used for treating disorders of the
parathyroid gland that result in abnormal blood calcium levels. It is well known to cause hypocalcemia and this risk is clearly outlined on the Canadian Sensipar® label.

Hypocalcemia can cause QT prolongation and arrhythmia which can be serious and may lead to sudden death. Stronger warnings have been added to the drug label to inform of the risk of QT prolongation and arrhythmia associated with use.

Healthcare professionals should prescribe cinacalcet with caution in patients with other risk factors for QT prolongation, such as known congenital long QT syndrome, or in patients who are taking other drugs known to cause QT prolongation. For patients treated with cinacalcet for chronic kidney disease and receiving dialysis, reduce dose or stop use if low blood calcium, signs of QT prolongation, or arrhythmia continue. For these patients, cinacalcet should not be started if they have severe hypocalcemia.


Ofatumumab and rituximab: reactivation of HBV infection

United States of America — The Food and Drug Administration (FDA) has approved changes to the prescribing information for ofatumumab (Arzerra®) and rituximab (Rituxan®) to warn of the risk of reactivation of hepatitis B virus (HBV) infection. The revised labelling will also include additional recommendations for screening, monitoring and managing patients. Both ofatumumab and rituximab are used to treat certain cancers of the blood and lymph system. Rituximab is also approved to treat other medical conditions, including rheumatoid arthritis. Both drugs suppress the immune system.

In patients with prior HBV infection, HBV reactivation may occur when the body’s immune system is impaired. Infection can cause serious liver problems, including liver failure and death. The risk of HBV reactivation is already described in the labelling for both drugs; however, cases continue to occur, including deaths.


Hydroxyethyl-starch solutions: only for hypovolaemia

European Union — The European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of hydroxyethyl-starch (HES) solutions following an assessment of new information and commitments from companies for additional studies and risk minimization activities. The Committee confirmed that HES solutions must no longer be used to treat patients with sepsis or burn injuries, or critically ill patients, because of an increased risk of kidney injury and mortality. HES solutions may, however, continue to be used in patients to treat hypovolaemia caused by acute blood loss, provided that appropriate measures are taken to reduce potential risks and that additional studies are carried out.

The review of HES solutions was initially triggered by the German medicines agency, the Federal Institute for Drugs and Medical Devices (BfArM), following studies showing an increased risk of mortality in patients with sepsis and an increased risk of kidney injury requiring dialysis in critically ill patients following treatment with HES solutions.

Artesunate: haemolytic anaemia

World Health Organization — Injectable artemisinin-based combination therapies (ACTs) are a life-saving therapy for patients with severe Plasmodium falciparum malaria and provide a substantial reduction of mortality. In the two largest randomized controlled trials conducted in patients with severe malaria, parenteral artemisinin treatment reduced deaths by 34.7% (Asia) and by 22.5% (Africa) compared with parenteral quinine. The updated indication states that ACTs are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

A number of cases of delayed haemolytic anaemia have been identified following treatment of severe malaria with injectable artemisinin. In March 2013, the Medicines for Malaria Venture (MMV) convened a meeting of experts to review the available evidence on delayed haemolytic anaemia following treatment with injectable artemisinin.

The full report of the expert meeting is now available on the MMV website together with an information note which reflects the current WHO position based on the outcome of the review meeting and consultation with the GMP Technical Expert Group on Malaria Chemotherapy.


Opioid analgesics: new safety warnings

United States of America — The Food and Drug Administration (FDA) has announced class-wide safety labelling changes and new postmarket study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain.

The updated indication states that ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The updated indication further clarifies that, because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain; ER/LA opioid analgesics are not indicated for as-needed pain relief.

The FDA is also requiring a new boxed warning on ER/LA opioid analgesics to caution that chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome.

Reference: FDA News Release, 10 September 2013 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements

Carbamazepine: HLA-B*1502 genotype testing

Singapore — The Ministry of Health (MOH) has announced that genotyping for the HLA-B*1502 allele prior to the initiation of carbamazepine (CBZ) therapy in new patients of Asian ancestry is now considered the standard of care. These new recommendations by MOH and the Health Sciences Authority (HSA) have been made in consultation with experts in various fields such as neurology, psychiatry and dermatology, following the review of findings from local and international studies.

Confirmed PRCA cases associated with epoetin alfa accounted for 90% of total epoetin alfa-associated PRCA cases in the HSA Pharmacovigilance database since the re-instatement of the subcutaneous route for Eprex® in April 2009. This is a disproportionately high number of PRCA cases reported compared to the baseline reporting trend.

During this period, nine PRCA cases were reported from two local healthcare institutions. All cases were reported with subcutaneous use of Eprex® in chronic kidney disease patients with duration of onset ranging from seven months to 19 months.


Sunitinib malate: cutaneous reactions

Canada — A statement has been added to the product monograph indicating a potential association between sunitinib malate (Sutent®) and severe cutaneous reactions suggestive of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). If signs or symptoms are present, treatment should be discontinued. If the diagnosis of SJS or TEN is confirmed treatment must not be restarted.

Sunitinib malate is indicated for the treatment of gastrointestinal stromal tumour after failure of imatinib mesylate treatment due to resistance or intolerance. It is also indicated for the treatment of metastatic renal cell carcinoma of clear cell histology and for the treatment of patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumours, whose disease is progressive.

CBZ has been registered in Singapore since 1988 and is currently available as Tegretol® and six generic products. It is indicated for the treatment of epilepsy and other conditions such as diabetic neuropathy, trigeminal neuralgia and bipolar disorders. While CBZ is an effective drug and the drug of choice for several conditions, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are associated with significant mortality and long-term morbidity, have been reported with its use.

Between 2003 and 2012, HSA received 131 local serious reports of CBZ-induced SJS/TEN (average of 15 reports per year). Since the beginning of 2013, HSA has received five reports of SJS/TEN associated with the use of CBZ. A one-time HLA-B*1502 genotyping test helps distinguish high-risk patients who should avoid CBZ from low-risk patients who are able to continue to use this low-cost yet effective medicine.

SJS and TEN often begin with flu-like symptoms, followed by development of a red or purplish rash and painful ulcers of mucous membranes. The skin lesions then progress to epidermal necrosis and detachment. These conditions require hospitalization and can be life-threatening and even fatal.


Epoetin alfa: increase in pure red cell aplasia

Singapore — The Health Sciences Authority (HSA) has advised of an unexpected increase in local cases of antibody-mediated pure red cell aplasia (PRCA) associated with subcutaneous administration of epoetin alfa (Eprex®) during the period 2012 and 2013.
Panitumumab: RAS status before treatment

United Kingdom — The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that evidence of wildtype rat sarcoma viral oncogene (RAS) status is required before initiating treatment with panitumumab (Vectibix®) alone or in combination with other chemotherapy in the treatment of metastatic colorectal cancer. Inferior progression-free survival and overall survival have been shown in patients with RAS mutations beyond KRAS exon 2 who received panitumumab combined with oxaliplatin-containing (Folfox®) chemotherapy versus Folfox® alone.

These findings emphasize that panitumumab is contraindicated in combination with oxaliplatin-based chemotherapy in patients with mutant RAS or in whom RAS status is unknown.


Fentanyl patches: colour changes to avoid exposure

United States of America — The Food and Drug Administration (FDA) is requiring colour changes to the writing on fentanyl (Duragesic®) pain patches in an effort to prevent accidental exposure. Used fentanyl patches require proper disposal after use.

FDA continues to learn of deaths from accidental exposure to fentanyl patches and is requiring the manufacturer to print the name and strength of the drug on the patch in long-lasting ink, in a color that is clearly visible to patients and caregivers.


Ornidazole: adverse eye effects

New Zealand — Since 1987, the Centre for Adverse Reactions Monitoring (CARM) has received 10 reports where the patient experienced eye problems — mainly described as visual impairment and blurred vision — following treatment with ornidazole, used to treat bacterial infections.

Visual impairment and/or blurred vision can affect the user’s ability to drive or operate machinery. Anyone experiencing these problems should not drive or operate machinery.


Statins: risk of acute kidney injury

New Zealand — Medsafe has identified a possible signal of acute kidney injury (without rhabdomyolysis) with the use of high-dose statins following a review of published literature. Myopathy or rhabdomyolysis is a well-known adverse effect of statin therapy, with acute kidney injury occurring secondary to these symptoms. Recent studies however have suggested that there is a risk of acute kidney injury occurring without prior or concurrent onset of myopathy or rhabdomyolysis. The overall benefit-risk balance of statins remains positive.

The Centre for Adverse Reactions Monitoring (CARM) has received a total of 38 reports which fulfil the criteria for acute kidney injury with statins. Of these, 24 also report rhabdomyolysis or creatine kinase elevations, which are suggestive of muscle problems.

Acute kidney injury is defined in different ways, from acute renal failure with tubular...
necrosis or unspecified, through to need for renal replacement therapy such as haemodialysis, peritoneal dialysis or kidney transplantation.


Low molecular weight heparin: risk of spinal column bleeding and paralysis

United States of America — The Food and Drug Administration (FDA) is recommending that health care professionals carefully consider the timing of spinal catheter placement and removal in patients taking anticoagulant drugs, such as enoxaparin, and delay dosing of anticoagulant medications for some time interval after catheter removal to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. These new timing recommendations, which can decrease the risk of epidural or spinal hematoma, will be added to the labelling of anticoagulant drugs known as low molecular weight heparins, including Lovenox® and generic enoxaparin products and similar products.

Health care professionals and institutions involved in performing spinal/epidural anesthesia or spinal punctures should determine, as part of a pre-procedure checklist, whether a patient is receiving anticoagulants and identify the appropriate timing of enoxaparin dosing in relation to catheter placement or removal. To reduce the potential risk of bleeding, consider both the dose and the elimination half-life of the anticoagulant:

For enoxaparin, placement or removal of a spinal catheter should be delayed for at least 12 hours after administration of prophylactic doses such as those used for prevention of deep vein thrombosis. Longer delays (24 hours) are appropriate to consider for patients receiving higher therapeutic doses of enoxaparin (1 mg/kg twice daily or 1.5 mg/kg once daily).

A post-procedure dose of enoxaparin should usually be given no sooner than 4 hours after catheter removal. In all cases, a benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.

Epidural or spinal hematomas are a known risk of enoxaparin in the setting of spinal procedures and are already described in warnings and precautions for Lovenox® and generic enoxaparin products. However, these serious adverse events continue to occur.

It is important to note that all anticoagulants carry the risk of causing spinal bleeding when used in conjunction with epidural/spinal anesthesia or spinal puncture.


Pazopanib: hepatotoxicity

Canada — Healthcare professionals have been reminded that pazopanib hydrochloride (Votrient®) is associated with hepatotoxicity including hepatic failure and fatalities.

Physicians are asked to monitor serum liver tests before initiation and during treatment. Testing of serum liver enzyme and bilirubin levels during treatment has increased in frequency and periodic monitoring should continue after month four.

Pazopanib hydrochloride is a tyrosine kinase inhibitor indicated for treatment of metastatic renal cell (clear cell) carcinoma as first-line systemic therapy or second line systemic therapy after
treatment with cytokines for metastatic disease. It is also indicated for treatment of patients with selective subtypes of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease, or who have progressed within 12 months after (neo) adjuvant therapy.

Concomitant use of pazopanib hydrochloride and statins should be undertaken with caution and close monitoring.


Regadenoson and adenosine: fatal cardiac reactions

United States of America — The Food and Drug Administration (FDA) has warned healthcare professionals of the rare but serious risk of heart attack and death with use of the cardiac nuclear stress test agents regadenoson (Lexiscan®) and adenosine (Adenoscan®).

Patients with signs or symptoms of unstable angina or cardiovascular instability may be at greater risk for serious cardiovascular adverse reactions.

Regadenoson and adenosine are approved for use during cardiac nuclear stress tests in patients who cannot exercise adequately. They cause blood to flow preferentially to the healthier, unblocked or unobstructed arteries. In some cases, this reduced blood flow can lead to a heart attack, which can be fatal.

Cardiac resuscitation equipment and trained staff should be available before administering regadenoson or adenosine.


Thiocolchicoside: risk of aneuploidy

European Union — The European Medicines Agency’s Committee on Human Medicinal Products (CHMP) has recommended that thiocolchicoside-containing medicines for use by mouth or injection should be restricted across the European Union.

These medicines are now recommended only as an add-on treatment for painful muscle contractures resulting from spinal conditions in adults and adolescents 16 years of age or older. In addition, the dose of thiocolchicoside by mouth or injection should be restricted.

The review of thiocolchicoside was triggered by the Italian medicines regulatory agency, AIFA, following new experimental evidence which suggested that thiocolchicoside was broken down in the body into a metabolite (M2 or SL59.0955) that could damage dividing cells, resulting in aneuploidy. Aneuploidy is a risk factor for harm to the developing fetus, reduced fertility in men and in theory could increase the risk of developing cancer.

Preparations for local application to the skin, which do not produce substantial levels of M2 in the body, are not affected by this review.


Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious or unexpected adverse drug reactions. A signal is defined as “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information”. All signals must be validated before any regulatory decision can be made.