Safety news

Safety warnings

Warfarin: calciphylaxis
United Kingdom – The MHRA has informed healthcare professionals about the conclusions of an EU-wide review which found that on rare occasions warfarin use might lead to calciphylaxis, including in patients with normal renal function. If calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping warfarin treatment.

Calciphylaxis, also known as calcific uraemic arteriolopathy, is a very rare but serious condition that causes vascular calcification and cutaneous necrosis. The mortality rate is high. The condition is most commonly observed in patients with known risk factors such as end-stage renal disease.

  PRAC recommendations on signals. EMA/PRAC/313187/2016. 26 May 2016.

Eltrombopag: potentially fatal liver injury
Canada – Health Canada has published a warning about the risk of severe liver toxicity associated with the systemic haemostatic medicine eltrombopag (Revolade®). This follows the identification of five cases fulfilling the criteria for severe drug-induced liver injury in a recent review of all clinical trial and post-marketing cases.

To mitigate the risk of severe hepatotoxicity and potentially fatal liver injury, healthcare professionals should: measure serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin before initiating eltrombopag, every two weeks during the dose adjustment phase, and then monthly following establishment of a stable dose. In patients with normal liver function, eltrombopag should be discontinued if ALT levels increase to ≥ 3 × upper limit of normal (ULN). In patients with elevations in transaminases before treatment, eltrombopag should be stopped if ALT levels increase to ≥ 3 × baseline or > 5 × ULN, whichever is the lower. The Canadian product monograph has been updated to reflect this new safety information. (1)

The risk of hepatotoxicity and precautions for use have also been included in the product information for eltrombopag approved in the EU. (2)

  (2) EMA Product information. Revolade -EMEA/H/C/001110 -IAIN/0034/G.

Etonogestrel implants: migration from insertion site
United Kingdom – The MHRA has issued a warning about rare reports of complications with etonogestrel (Nexplanon®) contraceptive implants. In rare cases, such implants have moved from the insertion site and reached the lung via the pulmonary artery. An implant that cannot be palpated at its insertion site in the arm should be located as soon as possible and removed at the
earliest opportunity. If an implant cannot be located within the arm, chest imaging should be performed. Correct subdermal insertion reduces the risk of these events.


Ombitasvir/paritaprevir/ritonavir: acute renal failure
Japan – Following reported cases of acute renal failure in patients treated with the hepatitis C medicine ombitasvir/paritaprevir/ritonavir (Viekirax®) in Japan, the Ministry of Health, Labour and Welfare (MHLW) has recommended updates to the product information to include the following advice: Before starting this drug and periodically during treatment, renal function tests should be performed. As renal function may suddenly deteriorate in particular in patients with decreased renal function and in patients concomitantly receiving calcium channel blockers, these patients should be carefully monitored. If any abnormalities are observed, the drug should be discontinued and appropriate measures should be adopted.


Blinatumomab: pancreatitis
Canada – Health Canada has informed health professionals about reported cases of life-threatening, sometimes fatal pancreatitis associated with the use of blinatumomab (Blincyto®) in clinical trial and post-market settings, and about new recommended precautions. The diagnosis of pancreatitis should be considered in patients treated with blinatumomab who experience severe upper abdominal pain accompanied with nausea, vomiting or abdominal tenderness. If pancreatitis is suspected, blinatumomab should be either temporarily interrupted or discontinued.

Blinotumumab is a monoclonal antibody approved in Canada for the treatment of adult patients with certain forms of relapsed or refractory acute lymphoblastic leukaemia. The Canadian product information has been updated to reflect this new safety information.

Health Canada Advisory, 13 July 2016.

Carmustine intracerebral implant: risk of air accumulation
Japan – The PMDA has informed health professionals that in patients receiving a carmustine (Gliadel®) intracerebral implant, air accumulation may occur at the implant site, and there have been reports of neurological symptoms. Accordingly, the Ministry of Health, Labour and Welfare (MHLW) has recommended updates to the product information for carmustine. After the implantation patients should be monitored for neurological symptoms, such as hemiplegia, aphasia, and disturbed consciousness, and appropriate measures adopted if any abnormalities are observed.

PMDA Summary of investigation results and MHLW Revisions of precautions, 5 July 2016.

Idelalisib: updated measures to manage risk of infections
European Union – The EMA has completed its review of idelalisib (Zydelig®), confirming that its benefits outweigh its risks in the treatment of two types of blood cancers, chronic lymphocytic leukaemia (CLL) and follicular lymphoma. Updated recommendations have been provided to manage the risk of serious infections which was also
confirmed by the review. All patients treated with idelalisib should be given antibiotics to prevent *Pneumocystis jirovecii* pneumonia during treatment and for up to 2 to 6 months thereafter. Patients should be monitored for infection and white blood cell counts should be performed regularly. Idelalisib should not be started in patients with a generalized infection.

A precautionary recommendation had initially been issued, advising against starting idelalisib treatment in patients with previously untreated CLL whose cancer cells have certain genetic mutations. The updated advice now allows initiation of idelalisib in these patients, provided that there are no alternative treatment options and that the recommended measures to prevent infection are followed.


**Opioids and benzodiazepines: potentially fatal side effects**

United States of America – An extensive FDA review has found that the growing combined use of opioid medicines with benzodiazepines or other central nervous system (CNS) depressants has resulted in serious side effects, including slowed or difficult breathing and deaths. A boxed warning and revisions to the *Warnings and Precautions, Drug Interactions,* and *Patient Counseling Information* sections have been included in the product information for opioid and benzodiazepine medicines class-wide.

Opioid pain medicines should only be prescribed together with benzodiazepines or other CNS depressants if alternative treatment options are inadequate. In such cases, the lowest possible dosage and duration of each drug should be used to achieve the desired clinical effect. Health professionals should warn patients and caregivers about the risks of slowed or difficult breathing and/or sedation and the associated signs and symptoms. The use of opioid cough medicines should be avoided in patients taking benzodiazepines or other CNS depressants, including alcohol.

► FDA Drug safety communication, 31 August 2016.
FDA News release, 31 August 2016.

**Levetiracetam: acute renal failure**

Japan – Revisions to the approved product information have been recommended for the anti-epileptic medicine levetiracetam (Keppra®) in Japan to warn about the risk of acute renal failure. This follows reported cases of acute kidney failure in patients treated with levetiracetam in Japan. Revised product information recommends that patients should be carefully monitored and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.


**Citalopram: suspected drug interaction with cocaine**

United Kingdom – The MHRA has advised health professionals to enquire about possible nonmedical drug use before prescribing medicines that have the potential to interact adversely with illicit drugs. This follows the death of a man from subarachnoid haemorrhage that raised concerns about a suspected drug interaction between the antidepressant
citalopram and cocaine. An expert group advised that hypertension related to cocaine and an additive increased bleeding risk in combination with citalopram could be plausible mechanisms for such an interaction.

Health professionals were also reminded of potential interactions between cocaine and selective serotonin reuptake inhibitors (SSRIs), and of the need to avoid concurrent use of multiple serotonergic drugs.


Restrictions

Riociguat: not for patients with pulmonary hypertension caused by idiopathic interstitial pneumonia

European Union, Canada – The EMA and Health Canada have reminded health professionals that the antihypertensive medicine riociguat (Adempas®) should not be used in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonia. A contraindication will be added to the product information to help ensure that the medicine is not used in this patient population.

The recommendation follows the early termination of a phase II clinical trial called RISE-IIP which was investigating the effects of the medicine in these patients. Preliminary results showed an increased number of deaths and serious adverse events, with no clinically significant benefit.

  MHRA Drug Safety Update volume 10 issue 1, August 2016: 1.

Fluoroquinolones: use only in certain serious infections

United States of America – The FDA has approved labelling changes to limit the use of fluoroquinolones in acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections to patients that have no other treatment options. This follows a warning communicated in May 2016 about the risk of disabling and potentially permanent serious side effects that can occur, including tendon inflammation and rupture, peripheral neuropathy, psychiatric reactions, photosensitivity, and prolongation of QTc interval. The benefits of fluoroquinolones continue to outweigh their risks in certain serious bacterial infections such as anthrax, plague and bacterial pneumonia.

► FDA News release, 26 July 2016.
  FDA Drug safety communication, 26 July 2016.

Known risks

Canagliflozin, dapagliflozin: kidney injury

United States of America – The FDA has strengthened its warnings about the risk of acute kidney injury associated with the type 2 diabetes medicines canagliflozin (Invokana®, Invokamet®) and dapagliflozin (Farxiga®, Xigduo XR®). Health professionals should consider individual risk factors for kidney injury and should assess kidney function before starting canagliflozin or dapagliflozin therapy. Kidney function should be monitored periodically thereafter. If acute kidney injury occurs, the medicine should...
be discontinued promptly and the kidney impairment treated.

► FDA Drug safety communication, 15 June 2016.

**Apixaban: Liver function disorder**

Japan – The Pharmaceuticals and Medical Devices Agency (PMDA) has informed health professionals that cases of liver function disorder have been reported in Japan in patients treated with the anti-thrombotic agent apixaban (Eliquis®). Based on these findings, the Ministry of Health, Labour and Welfare (MHLW) has recommended changes to the product information stating that hepatic function disorder associated with increased levels of AST (GOT), ALT (GPT) and other findings in liver function tests may occur, and that patients should be carefully monitored. If any abnormalities are observed, administration of apixaban should be discontinued and appropriate measures should be taken. (1)

Elevation of liver transaminases are also listed as adverse reactions in the product information for apixaban approved in the European Union. (2)

► (1) PMDA Summary of investigation results and MHLW Revisions of precautions, 5 July 2016.

► (2) EMA. Eliquis : EPAR - Product Information. Last updated 15 April 2016.

**Clarification of indications**

**Fingolimod: not proven in progressive multiple sclerosis**

Japan – The PMDA has recommended updates to the product information for fingolimod (Gilenya®) to clarify the precautions concerning its indications. The product is approved in Japan to prevent relapse and to delay accumulation of physical disability in multiple sclerosis.

Wording has been added to the product information stating that fingolimod did not slow progression of physical disability in an overseas placebo-controlled study in patients with primary progressive multiple sclerosis, and providing an overview of the findings and a reference to the published study.


**Medical device-related**

**Blood clotting time measuring devices: inaccurate readings**

Canada – Alere Inc. has withdrawn the Alere INRatio® and INRatio®2 Prothrombin Time Monitoring Systems (professional and self-test) devices from the Canadian market. These devices measure blood clotting time in patients requiring warfarin and other oral blood-thinning medicines.

There is a risk that the devices provide an inaccurate low reading. This could result in an improper dosage of warfarin or other blood-thinning medications being administered, leading to excessive bleeding with potentially serious adverse outcomes.


TGA Alert, 21 July 2016.

**N-acetylcysteine and biochemistry assays**

United Kingdom – The MHRA has advised health professionals who are treating patients with N-acetylcysteine for paracetamol overdose to establish whether Siemens ADVIA Chemistry and
Dimension/Dimension Vista instruments are used for laboratory testing of biochemistry. If so, they should do venipuncture and blood sampling before N-acetylcysteine administration, as there is a risk of false low biochemistry test results if blood is sampled during or immediately after administration. When requesting biochemistry tests (such as cholesterol, uric acid, lactate) that include any affected assays from these instruments, health professionals should state that a patient is receiving N-acetylcysteine.

► Drug Safety Update volume 9 issue 12, July 2016: 3.
MHRA Medical safety alert, 22 June 2016 (includes a full list of affected assays).

### Medicines safety reviews started

<table>
<thead>
<tr>
<th>Product</th>
<th>Use</th>
<th>Concerns</th>
<th>Reviewing authority reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dapagliflozin, empagliflozin</strong> (extension of the ongoing review of canagliflozin)</td>
<td>Treatment of type 2 diabetes</td>
<td>Increase in amputations mostly affecting toes reported in the ongoing CANVAS trial.</td>
<td>EMA News, 8 July 2016.</td>
</tr>
<tr>
<td><strong>Factor VIII-containing medicines</strong></td>
<td>Treatment of haemophilia A</td>
<td>Increased risk of developing inhibitor proteins. A recent study has suggested that this risk is higher with factor VIII medicines made by DNA recombinant technology than those derived from blood.</td>
<td>As above</td>
</tr>
<tr>
<td><strong>Modified- and prolonged release paracetamol</strong></td>
<td>Analgesic</td>
<td>Possible need to develop dosage form-specific standard procedures for assessing and managing overdose</td>
<td>As above</td>
</tr>
<tr>
<td><strong>Retinoid medicines</strong> (acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tazarotene and tretinoin)</td>
<td>Treatment of skin conditions, including acne and psoriasis. Some retinoids are used to treat certain forms of cancer.</td>
<td>Need to evaluate current measures for pregnancy prevention and for minimizing the possible risk of neuropsychiatric disorders.</td>
<td>As above See also: Health Canada Advisory, 7 September 2016.</td>
</tr>
</tbody>
</table>
Non-compliance with good practices

This section provides an overview of recent warnings and alerts issued as a result of inspection findings. Increasingly, such findings have led to concerns about data integrity. The reasons are diverse and include the increased use of computerized systems in pharmaceutical development and manufacturing, improved capacities of inspectors, and a lack of awareness among manufacturers of the significance of data integrity and regulatory expectations (1).

This has prompted the development of new regulatory guidance on data integrity, including finalized EMA guidance (see page 401), draft FDA guidance (2) and draft MHRA guidance (see page 404). In 2015, WHO issued a new guidance text – the first international text – on good data and record management practices (3). It consolidates the normative principles into one comprehensive document and gives detailed examples of how they can be implemented. In delivering the 2016 MHRA annual lecture, the WHO Director-General thanked international experts who contributed to this guidance, saying that it will “help reduce incidents of incomplete presentation of data by manufacturers or deliberate data falsification” (4).

► (1) WHO Essential medicines and health products news, 3 June 2016.

Alkem Laboratories Ltd, India: data integrity issues

European Union – The EMA concluded its review of medicines for which studies have been conducted by Alkem Laboratories Ltd, and has announced that bioequivalence studies conducted at the Alkem site in Taloja, India, cannot be used to support marketing authorization in the EU. A riluzole-containing product has been suspended, and an ibuprofen-containing product will be refused authorization until alternative data are presented from other sources. For three other antibiotic products – two authorized products and one under evaluation – alternative bioequivalence data have been provided.

The recommendations follow a joint routine inspection by German and Dutch authorities in March 2015, which revealed misrepresentation of data in two different trials performed in 2013 and 2014 at the Taloja site. The findings cast doubts on the quality management system in place at the site, and thus on the reliability of the data of bioequivalence studies conducted between March 2013 and March 2015.


Quest Life Sciences Pvt Ltd, India: data integrity issues

United Kingdom – The MHRA has suspended the marketing authorization of a generic erythromycin product that had been approved based on clinical trials conducted by India’s Quest Life Sciences. This follows an MHRA inspection of the Quest Life Sciences site in February 2016, which revealed several data integrity issues. Four other pending applications for marketing authorization that rely on studies conducted by Quest Life Sciences may be rejected. This affects products
containing doxycycline, cephalexin and metformin. (1)

The WHO Prequalification Team (PQT) had issued a notice of concern to Quest Life Sciences in July 2015. (2)

► (1) UK drugs regulator halts approvals for Indian clinical trials firm. Reuters, 1 July 2016.
(2) WHO Prequalification update, 3 July 2015.

Semler Research Centre Pvt Ltd, India: EMA review concluded
European Union – The EMA has concluded its review of Semler Research Centre Private Ltd, Bangalore, India, and has recommended suspending a number of nationally approved medicines for which bioequivalence studies were conducted at Semler. National authorities can postpone the suspension for medicines of critical importance. Furthermore, medicines still under evaluation cannot be granted authorization in the EU on the basis of studies conducted at Semler. (1)

The review followed an FDA inspection that identified several issues at Semler’s bioanalytical site, including the substitution and manipulation of subjects’ clinical samples. The FDA had notified pharmaceutical companies that studies conducted at Semler are unacceptable to support approval of medicines (2).

The WHO Prequalification Team had also raised serious concerns regarding data integrity and manipulation of study samples following its own inspections of Semler’s bioanalytical and clinical sites. A WHO Notice of Concern was issued to Semler in April 2016 (3).

► (1) EMA Press release, 22 July 2016.
(2) FDA Notification to pharmaceutical companies, 20 April 2016.
(3) WHO Notice of Concern, 12 April 2016.

Zhejiang Medicine Co Ltd, China: unreported impurity testing results
United States of America – The FDA has issued a warning letter to Zhejiang Medicine Co. Ltd as a follow-up to observations made an inspection of its Xinchang Pharmaceutical Factory in June 2015. The investigators had found chromatograms from unofficial testing, showing large unknown peaks of uncharacterized impurities, including potential contaminants, in the active pharmaceutical ingredients (APIs) tested. These results were not reported in the official records for the API samples. In addition, worksheets were found to have been backdated, and actions were not traceable to specific individuals due to failures in the company’s data integrity systems. The company was requested to conduct a comprehensive investigation into the extent of the failures and a risk assessment of their potential effects.

In August 2016, the FDA Center for Drug Evaluation and Research also issued warning letters to the API manufacturer Unimark Remedies Ltd, India over similar deficiencies (2), the finished product manufacturer Huzhou Aupower Sanitary Commodity Co., Ltd, Zhejiang, China (3), the API manufacturer Xinxiang Tuoxin Biochemical Co. Ltd, Henan, China (4), and the finished product manufacturers Pan Drugs Ltd, Vadodara, India (5), and Lima & Pergher Industria e Comercio S/A, Minas Gerais, Brazil (6). All FDA warning letters are available on the Agency’s website (7).

► (1) FDA Warning letter, 4 August 2016.
(2) FDA Warning letter, 12 August 2016.
(3) FDA Warning letter, 10 August 2016.
(4) FDA Warning Letter, 19 August 2016.
(7) www.fda.gov/ICECI/EnforcementActions/WarningLetters/
Pharmaceutics International Inc., U.S.: non-compliance with GMP

European Union – The EMA has started a review of medicines manufactured by Pharmaceutics International Inc., USA, following several shortcomings observed in good manufacturing practice (GMP) inspections conducted by the MHRA in June 2015 and February 2016. The shortcomings included insufficient measures to reduce the risk of cross-contamination, as well as deficiencies in data management and quality assurance systems.

Pharmaceutics International Inc. manufactures sodium phenylbutyrate (Ammonaps®), which is centrally authorized in the EU, and a number of nationally authorized medicines.


Shanghai Desano Co Ltd, China: non-compliance with GMP

United States of America – The FDA has issued a warning letter to the active pharmaceutical ingredients (API) manufacturer Shanghai Desano Chemical Pharmaceutical Co Ltd following findings on non-compliance with good manufacturing practices (GMP) during an inspection conducted at the site in Laogang Town, Pudong District, in May 2015. No import alert has been issued by the FDA. (1)

In response to the issuance of the FDA warning letter, the WHO Prequalification Team has requested manufacturers of prequalified products that use API manufactured by Shanghai Desano to take additional measures such as comprehensive testing upon receipt, to help ensure that the quality of all API batches is assured. (2)

► (1) FDA Warning letter, 16 June 2016.
(2) WHO PQT Information note, 5 July 2016.

Laxachem Organics Pvt Ltd, India: import ban for refusal of inspection

United States of America – The FDA has issued an import alert for products from Laxachem Organics Pvt. Ltd., Ahmednagar, Maharashtra, India, because the company has refused to allow FDA investigators to inspect its facility. Laxachem manufactures active pharmaceutical ingredient (API) for repackers, labelers and wholesale drug distributors.

According to the company’s website, one of the APIs supplied by Laxachem is docusate sodium. A voluntary nationwide recall of oral liquid docusate sodium from a domestic manufacturer had been organized in the United States in July due to contamination with *Burkholderia cepacia*, a bacteria linked to an outbreak in five U.S. states. This was followed by a voluntary recall of all liquid products by that manufacturer.

► FDA Update, 15 August 2016.
Falsified medicines

Falsified quinine sulphate circulating in West and Central Africa

Geneva – WHO has issued a Medical Product Alert relating to the recent circulation of two confirmed falsified versions of quinine sulphate circulating in Cameroon and the Democratic Republic of the Congo, containing zero active pharmaceutical ingredient.

Quinine sulphate is used for the treatment of *P. falciparum* malaria in the region.

The products were first discovered by a local non-governmental organization. They failed field screening and were submitted to a WHO-prequalified quality control laboratory. Subsequent analysis showed that neither product contained any of the stated active pharmaceutical ingredient.

Details of the products are shown below.

<table>
<thead>
<tr>
<th>Product discovered in Cameroon:</th>
<th>Product discovered in Bunia, Dem. Rep. of the Congo:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product name:</td>
<td>Quinine Sulphate 300mg</td>
</tr>
<tr>
<td>Number of tablets per container:</td>
<td>Quinine Sulphate 300mg</td>
</tr>
<tr>
<td>Batch number:</td>
<td>F4387</td>
</tr>
<tr>
<td>Expiry Date:</td>
<td>11/18</td>
</tr>
<tr>
<td>Date of manufacture:</td>
<td>12/14</td>
</tr>
<tr>
<td>Stated manufacturer:</td>
<td>CAD Pharm, India</td>
</tr>
</tbody>
</table>

WHO requests increased vigilance within the supply chains of countries likely to be affected by these falsified products. Increased vigilance should include hospitals, clinics, health centres, pharmacies and any other suppliers of medical products. Health authorities are asked to immediately notify WHO if these falsified products are discovered in their country. Any information on their supply and/or distribution should be sent to rapidalert@who.int.

► [WHO Medical Product Alert No. 4/2016 (includes photographs)].