Safety news

Restrictions

Repaglinide: contraindicated with clopidogrel
Canada – Health Canada has approved a new contraindication for the anti-diabetic medicine repaglinide (Gluconorm® and generics). Repaglinide must not be administered concomitantly with clopidogrel, a known inhibitor of the CYP2C8 pathway through which repaglinide is predominantly metabolized. Co-administration of repaglinide and clopidogrel may lead to significant decreases in blood glucose levels. The product information for the two medicines is being updated.

Safety warnings

Sitagliptin, saxagliptin, linagliptin, alogliptin: severe joint pain
United States of America – The US Food and Drug Administration (FDA) has warned that the anti-diabetic medicines sitagliptin, saxagliptin, linagliptin and alogliptin may cause joint pain that can be severe and disabling.

These medicines belong to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors and are approved for treatment of type-2 diabetes. A new warning about this risk has been added to the product information of all FDA-approved products containing a DPP-4 inhibitor.
► FDA Drug safety communication, 28 August 2015.

Anagliptin: intestinal obstruction
Japan – Cases of intestinal obstruction have been reported in patients treated with the anti-diabetic anagliptin (Suiny®) in Japan. The Pharmaceutical and Medical Devices Agency (PMDA) has requested updates to the product information to warn about this risk, and to advise caution when using it in patients who have a history of abdominal surgery or intestinal obstruction.
► PMDA Summary of investigation results, 7 July 2015.

SGLT2 inhibitors: atypical diabetic ketoacidosis
European Union, New Zealand, Australia – The marketing authorization holders, in consultation with the competent regulatory authorities (1, 2, 3) have advised health professionals to test for raised ketones in patients presenting with acidosis symptoms and treated with a sodium glucose co-transporter 2 (SGLT2) inhibitor, even if plasma glucose levels are near-normal. This follows reports of serious cases of diabetic ketoacidosis associated with SGLT2 inhibitors, including some atypical ones where blood glucose levels were only moderately increased.

SGLT2 inhibitors such as canagliflozin, dapagliflozin and empagliflozin are approved for treatment of type-2 diabetes. They are under review by several...
regulatory authorities for their possible association with ketoacidosis (4, 5, 6).

► (1) MHRA Drug safety update, 26 June 2015.
(2) MedSafe safety information; letter to health care professionals, 3 July 2015.
(3) TGA Safety advisory, 13 August 2015.
(4) FDA Safety announcement, 5 May 2015.
(6) PMDA Risk communication, 21 August 2015.

Epoetin beta: possible increased risk of retinopathy in preterm infants
United Kingdom – The Medicines and Healthcare Products Regulatory Agency (MHRA) has recommended that health professionals should carefully consider the benefits and risks of epoetin beta (NeoRecormon®) in preventing anaemia of prematurity, as a European review has identified a possible risk of retinopathy. More data will be needed to draw a firm conclusion. The product information in the EU will be amended to include this information.

► Drug Safety Update volume 8 issue 10 May 2015: 3.

Adefovir pivoxil: fractures
Japan – The PMDA has warned about an increased risk of fractures in patients treated with the anti-hepatitis-B medicine adefovir pivoxil (Hepsera®). A total of 43 cases of fractures were reported in Japan during the last three fiscal years; the causal relationship with the fractures was not evaluated. The product information has been updated to warn about this risk and to recommend measures to prevent hypophosphataemia, which can lead to osteomalacia and can thus increase the risk of fractures.

► PMDA Summary of investigation results, 7 July 2015.

Ingenol mebutate: severe allergic reactions and herpes zoster
United States of America – The FDA has warned about reports of severe allergic reactions and herpes zoster (shingles) associated with the use of ingenol mebutate gel (Picato®) used to treat actinic keratosis.

Severe eye injuries and skin reactions have also been reported with the use of ingenol mebutate gel. In some of these cases the product was used on larger areas or for a longer period than instructed on the label, or was applied near the mouth, lips or eyes, or was transferred from the hands through application of make-up and insertion of contact lenses.

The FDA is requiring changes to the label to warn about these new safety risks and to provide additional instructions on the safe application of the product.

► FDA Drug safety communication, 21 August 2015.

Asunaprevir, daclatasvir: decreased hepatic residual function
Japan – The PMDA has warned about cases of decreased hepatic residual function in patients treated with asunaprevir (Sunvepra®) and daclatasvir (Daklinza®) for hepatitis C infection. Patients presented with decreased albumin level, prolonged prothrombin time, ascites and/or hepatic encephalopathy, potentially leading to hepatic failure. In the last three years 21 such cases, including one fatal case, were reported in Japan in which an association with asunaprevir
and daclatasvir combination therapy could not be ruled out. The product information for the two medicines has been revised accordingly.

► PMDA Investigation results, 7 July 2015 and MHLW Revisions of precautions, 7 July 2015.

Influenza HA vaccine: optic neuritis
Japan – The PMDA has requested updates to the product information for four influenza haemagglutinin (HA) vaccine products to reflect the risk of optic neuritis. This follows reports of optic neuritis in people who received this vaccine in Japan, including three cases where causality could not be ruled out.

► PMDA Summary of investigation results. 7 July 2015.

Abiraterone acetate: fulminant hepatitis, hepatic failure
Japan – The PMDA has recommended to revise the package insert of abiraterone tablets (Zytiga®), used to treat castration-resistant prostate cancer, to warn about the risk of fulminant hepatitis and hepatic failure. EMA-approved product information mentions the risk of hepatotoxicity with elevated alanine aminotransferase (ALT), aspartate transaminase (AST) and total bilirubin in patients treated with abiraterone.

► PMDA Summary of investigation results. 7 July 2015.

Fingolimod: progressive multifocal leukoencephalopathy
United States of America – The FDA has updated the product information for fingolimod (Gilenya®) to warn about a confirmed and a probable case of confirmed progressive multifocal leukoencephalopathy (PML) in patients treated for multiple sclerosis who had not previously received any immunosuppressants (1). PML is a rare and serious brain disease caused by reactivation of the John Cunningham (JC) virus in patients with a weakened immune system.

In April 2015 the EMA and marketing authorization holders had warned health professionals about this risk (2), and the PMDA of Japan has meanwhile started a safety review (3).

► (1) FDA Drug safety communication, 4 August 2015.
► (3) PMDA Risk communication, 21 August 2015.

Methylphenidate patches: permanent skin discolouration
United States of America – The FDA is warning that permanent loss of skin colour, known as chemical leukoderma, may occur with the use of the methylphenidate transdermal system (Daytrana® patch) to treat attention deficit hyperactivity disorder (ADHD). Chemical leukoderma is not physically harmful but is thought to be irreversible, which may cause emotional distress.

A new warning has been added to the drug label. The FDA is recommending that patients and caregivers should be instructed to watch out for new areas of lighter skin especially under the drug patch, and health care professionals should consider alternative treatments if such changes are reported.

► FDA Drug safety communication, 24 June 2015.
**Diazoxide: pulmonary hypertension**  
**United States of America** – The FDA has warned about a serious lung condition occurring in infants and newborns treated with diazoxide (Proglycem®) for low blood sugar. In all cases, the pulmonary hypertension resolved or improved after diazoxide was stopped. The FDA is investigating this safety issue and will determine whether changes are needed in the product information.

Diazoxide is usually given in the hospital. Health care professionals should closely monitor infants receiving it, especially those with risk factors for pulmonary hypertension, and treatment should be stopped if the condition is identified. Parents and caregivers should be instructed to alert a health professional immediately if they notice signs of difficult breathing in their child.

► **FDA Drug Safety Communication, 16 July 2015.**

**General use syringes: not to be used to store medicines**  
**United States of America** – The FDA has warned health care professionals not to administer to patients any compounded or repackaged drugs that have been stored in 3ml and 5ml syringes manufactured by Becton-Dickinson (BD) unless there is no suitable alternative available. Preliminary information indicates that medicines (such as fentanyl, morphine, methadone and atropine) stored in these syringes may lose potency over time due to a possible interaction with the rubber stopper in the syringe.

The syringes have been cleared by the FDA as medical devices for general purpose fluid aspiration and injection only, not for use as a closed container storage system for drug products. This issue may extend to general use syringes made by other manufacturers. The warning does not extend to products approved by FDA for marketing as pre-filled syringes.

► **FDA Drug alert, 18 August 2015.**

**Known risks**

**Ivabradine: heart problems in patients with angina**  
**Australia** – The Therapeutic Goods Administration (TGA) has completed a safety review of ivabradine (Coralan®), and has recommended measures to reduce the risk of cardiovascular events in patients with angina. Patients who take ivabradine for angina must now have a resting heart rate of at least 70 beats per minute (increased from 60 beats per minute). Ivabradine should not be taken in combination with diltiazem and verapamil, and an existing warning has been strengthened to advise that drinking grapefruit juice should be avoided (rather than ‘restricted’).

In November 2014 the EMA had recommended similar measures to reduce the risk of heart problems with ivabradine.

► **TGA safety advisory, 9 July 2015.**  
EMA. **European Medicines Agency recommends measures to reduce risk of heart problems with Corlentor/Procoralan (ivabradine). 15 January 2015.**

**Indapamide: toxic epidermal necrolysis**  
**Japan** – Following reports of toxic epidermal necrolysis in patient treated with the antihypertensive indapamide (Natrix®, Tenaxil®) in Japan, including a fatal case where a causal relationship could not be ruled out, the PMDA has updated the product information for this medicine to
warn about this risk. Product information in the EU already carries a warning about this adverse reaction, classifying it as very rare.
► PMDA Summary of investigation results, 7 July 2015.

NSAIDs: heart attack or stroke
United States of America – The FDA has strengthened its warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, diclofenac and celecoxib, can cause heart attacks or strokes. These events can occur from the first weeks of using an NSAID, and can occur in patients without heart disease or cardiovascular risk factors. The risk may increase with longer use and appears to be greater at higher doses. Patients and health care professionals should remain alert for heart-related side effects for the entire time that NSAIDs are being taken. The FDA is requiring updates to the product information of all prescription NSAIDs, and will also request updates to the over-the-counter non-aspirin NSAID Drug Facts labels. (1)

New Zealand – Medsafe has concluded its consultation on the proposed addition of warning statements on labels of over-the-counter oral and topical diclofenac medicines. The updated statements for oral formulations include warnings about their cardiovascular risks. (2)

(2) Medsafe News, 19 August 2015.

Paracetamol: additional measures for safe use
Canada – Based on its review of liver injury and paracetamol (U.S. adopted name: acetaminophen) in Canada, and following strengthened labelling standards introduced in 2009, Health Canada is taking additional steps to improve paracetamol safety.

With over 4 billion doses of paracetamol sold annually, the number of approximately 250 cases of serious liver injury reported each year in Canada can be considered to be relatively low. Over half of the reported cases involved accidental overdose, pointing to a need for clearer warnings. Health Canada will propose a draft revised labelling standard for non-prescription paracetamol-containing products for comment later this year.

Unchanged recommendations
New anti-coagulants: No evidence to support routine blood monitoring
Australia – A recently completed TGA review has found that there is currently no evidence to support a recommendation for routine blood monitoring in patients treated with the new oral anticoagulants apixaban (Eliquis®), dabigatran (Pradaxa®) and rivaroxaban (Xarelto®). Plasma monitoring may be useful in some clinical circumstances, such as overdose or emergency surgery.

The TGA undertook the review following recent publication of articles in the medical literature which suggested that the safety of these medicines could be improved if routine blood monitoring was undertaken.
► TGA News, 4 June 2015.
Safety reviews started

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<td>The review does not question that the benefits of HPV vaccines outweigh their risks. It focuses on rare reports of complex regional pain syndrome and postural orthostatic tachycardia syndrome.</td>
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<td>Codeine</td>
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WHO Notices of Concern

**Quest Life Sciences**

Geneva – Following its inspection of the contract research organization (CRO) Quest Life Sciences Pvt Ltd in October 2014, which revealed some critical and major deviations from good clinical practice and good manufacturing practice, the WHO Prequalification Team (PQT) has published a Notice of Concern about this site (1). Swissmedic has responded by stating that no medicines marketed in or exported from Switzerland have been studied at Quest Life Sciences. (2)

► (1) WHO Prequalification update, 3 July 2015.
► (2) Swissmedic announcement, 29 July 2015.

**Svizera Labs Pvt Ltd**

Geneva – A WHO Notice of Concern has been issued to Svizera Labs Pvt Ltd in India, which has had three anti-tuberculosis medicines prequalified by WHO. The company has been asked to correct several critical and major deviations from good manufacturing practices and data integrity problems observed during a WHO inspection in June 2014.

As with all WHO Notices of Concern, the full text of the request addressed to the company is available on the WHO Prequalification Team’s website.

► Prequalification update, 3 September 2015.
Falsified product alert

Falsified diazepam in Central Africa

Geneva — WHO has published a Medical Product Alert about the confirmed circulation of two versions of falsified versions of diazepam tablets circulating in Central Africa.

Since December 2014, over 400 patients in the North East region of the Democratic Republic of Congo (DRC) have suffered from an acute dystonic reaction affecting the muscles of the face, neck and tongue. The adverse effect has resulted in up to 40 hospital admissions per week. So far, all known patients suffering a reaction have recovered.

One of the products has been analysed in the laboratory and was found to contain no diazepam, but between 10mg to 20mg of haloperidol per tablet. Haloperidol is an antipsychotic used primarily for the treatment of schizophrenia, and has a known risk of acute dystonic reactions affecting the face and neck. Without treatment this reaction usually lasts 3 to 4 days, and it sometimes re-occurs. Although all known patients have recovered, the levels of haloperidol present in the tablets pose a serious risk particularly to the young. – A detailed investigation carried out in DRC has revealed that patients had been taking diazepam to treat a wide range of illnesses.

► WHO Medical Product Alert No. 4/2015, 2 July 2015 (with photographs).

The U.S. FDA has warned consumers not to purchase diazepam online due to the potentially serious counterfeiting issue reported in the WHO Medical Product Alert of 2 July 2015.

► FDA Drug alert, 2 July 2015.

PRODUCT ONE: This product is circulating in the Ituri Health District of the Democratic Republic of Congo and the adverse reactions have been focused in the vicinity of Nono. Laboratory analysis has shown that the product does not contain diazepam, but contains between 10mg to 20mg of haloperidol per tablet. WHO is requesting urgent vigilance for these tablets.

- Stated trade name: SOLINA
- Stated Product: Diazepam BP 5 mg
- Appearance: Light yellow tablets, scored across the centre on one side and bearing the letters AGOG on the other side
- Packaging: Plastic bottle of 1000 tablets stamped in red ink ‘Government of Uganda. For public use only, not for sale’.
- Labelling: Batch Number: SBG038
- Manufacturing Date: Sep 2014
- Expiry Date: Aug 2017
- Stated manufacturer: Centaur Pharmaceuticals

The pharmaceutical manufacturer AGOG has stated that they manufacture haloperidol tablets which are yellow in colour and bear the letters AGOG. However, these are supplied in blisters of 10 tablets and boxes of 10 blisters under the trade name AGOHAL, Haloperidol tablet BP 10mg. AGOG Pharma Ltd have stated that they do not manufacture diazepam.

CENTAUR pharmaceuticals have confirmed that they manufacture diazepam and that the batch number, dates of manufacturing and expiry as shown on the falsified packaging correspond to correct existing batch numbers and dates. CENTAUR Pharmaceuticals have stated that they do not manufacture haloperidol. The tablets contained in the plastic bottles and marked AGOG were not manufactured by CENTAUR Pharmaceuticals.

PRODUCT TWO: This falsified diazepam product is also circulating in the Democratic Republic of Congo. The tablets have not yet undergone laboratory analysis, but confirmation has been received that the labelling is falsified. WHO requests increased vigilance for the product.

- Stated trade name: DIAZPAM TABLETS
- Stated Product: Diazepam BP 5 mg
- Appearance: Light yellow tablets, scored across the centre on one side and bearing the letters AGOG on the other side
- Packaging: Container of 1000 tablets
- Labelling: Batch Number: 2332
- Manufacturing Date: Nov 2013
- Expiry Date: Oct 2016
- Stated manufacturer: Centaur Pharmaceuticals

The pharmaceutical manufacturer AGOG Pharma have confirmed that this packaging and labelling is falsified. AGOG Pharma have confirmed they do not manufacture diazepam.

CENTAUR Pharmaceuticals have confirmed that they manufacture diazepam and that the batch number, date of manufacturing and expiry as shown on the falsified packaging correspond to correct existing batch numbers and dates. The tablets contained in the plastic bottles and marked AGOG were not manufactured by CENTAUR Pharmaceuticals.