

Safety news

Restrictions

Bromhexine: not to be used in children under six in New Zealand

New Zealand – Following international reports of rare but serious allergic reactions (including anaphylaxis and severe skin reactions) associated with the use of bromhexine, the regulatory authority of New Zealand, Medsafe, has recommended that bromhexine-containing medicines to treat cough and cold symptoms should only be used in adults and children six years of age and over as there is not enough evidence to support their use in younger age groups.

In February 2015, the EMA had warned about these risks and had recommended that they should be included in product information of bromhexine and ambroxol (the active metabolite of bromhexine).

► [Medsafe Safety information, 29 April 2015.](#)

Codeine for cough and cold: not to be used in children under 12

European Union – The European Medicines Agency (EMA) has concluded its review of codeine-containing cough and cold medicines in children and has recommended further restrictions to minimize the risk of morphine-induced side effects, such as breathing problems, that occur due to the conversion of codeine into morphine in the body.

Codeine should never be used in children below 12 years. Its use to relieve cough and cold is not recommended

in children and adolescents between 12 and 18 years who have problems with breathing. All liquid codeine medicines should be available in child-resistant containers to avoid accidental ingestion.

In 2013 the EMA had reviewed the risks and benefits of using codeine for pain relief in children, and had recommended similar restrictions. (1)

New Zealand – Medsafe has warned about the above-mentioned risks and has recommended to restrict the use of codeine-containing products for cough and cold symptoms to adults and children 12 years of age and over. (2)

► (1) [EMA Press release, 24 April 2015.](#)

(2) [Medsafe Safety information, 29 April 2015.](#)

Safety warnings

Sitagliptin: thrombocytopenia

Japan – The Pharmaceuticals and Medical Devices Agency (PMDA) has warned about cases of thrombocytopenia reported in patients treated with the anti-diabetic medicine sitagliptin hydrate (Glactiv®, Januvia®) in Japan, and has recommended to update the product information for these medicines. Patients should be monitored, and in case of abnormalities the drug should be discontinued and appropriate measures should be taken.

► [PMDA Summary of investigation results and Revisions of precautions, 24 March 2015.](#)

SGLT2 inhibitor diabetes medicines: ketoacidosis

United States of America – The U.S. Food and Drug Administration (FDA) has warned that serious cases of ketoacidosis have been reported in the United States in patients treated with the sodium-glucose cotransporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin. These medicines are approved to treat type-2 diabetes and are available as single-ingredient products and in combination with other diabetes medicines such as metformin. The FDA is investigating whether changes are needed in the prescribing information for these products.

Patients taking SGLT2 inhibitors who have symptoms of ketoacidosis (difficulty breathing, nausea, vomiting, abdominal pain, confusion, unusual fatigue or sleepiness) should be evaluated. If ketoacidosis is confirmed, health professionals should discontinue the SGLT2 inhibitors and take appropriate measures to correct the acidosis and monitor blood sugar levels.

► [FDA Safety announcement, 5 May 2015.](#)

Hepatitis C drugs and amiodarone: symptomatic bradycardia

United States of America – Following reports of symptomatic bradycardia in patients taking hepatitis C medicines and the antiarrhythmic drug amiodarone, the FDA has warned that serious slowing of the heart rate can occur when amiodarone is taken together with either ledipasvir/sofosbuvir (Harvoni®) or with sofosbuvir (Sovaldi®) and another direct acting antiviral, such as the investigational drug daclatasvir or simeprevir (Olysio®). Where alternative treatment options are

unavailable, the FDA recommends heart rate monitoring in an inpatient hospital setting for the first 48 hours, followed by daily monitoring by a doctor or the patient during at least the first two weeks of treatment.

Warnings have been added to the product information and patient leaflet for ledipasvir/sofosbuvir and for simeprevir. The FDA will continue to monitor the risk and investigate the reason for the adverse events. (1)

Canada – Health Canada has warned that postmarketing cases of symptomatic bradycardia, including two cases that occurred in Canada, have been reported in patients taking amiodarone with the above-mentioned hepatitis C products. Co-administration of amiodarone with Harvoni™ or Sovaldi® in combination with another direct-acting antiviral is not recommended.

The regulatory authority is working with the manufacturer to update the product monographs for Harvoni™ and Sovaldi® to reflect this new information. (2)

European Union – An EMA review conducted as a result of a safety signal has confirmed a risk of severe bradycardia or heart block when sofosbuvir with ledipasvir (Harvoni®) or a combination of sofosbuvir (Sovaldi®) and daclatasvir (Daklinza®) are used in patients who are also taking amiodarone.

To manage this risk the EMA recommends that in patients taking these hepatitis C medicines amiodarone should only be used if other antiarrhythmics cannot be given, and only with close monitoring. Due to the long half-life of amiodarone monitoring is also needed in patients starting such hepatitis C

treatments within a few months of stopping amiodarone. (3)

- ▶ (1) [FDA Safety Announcement, 24 March 2015](#).
- (2) [Health Canada Advisory, 2 April 2015](#).
- (3) [EMA Press release, 24 April 2015](#).

Asunaprevir and daclatasvir: erythema multiforme

Japan – The PMDA has warned that cases of erythema multiforme have been reported in patients treated concomitantly with daclatasvir (Daklinza®) and asunaprevir (Sunvepra®) in Japan. The two products are approved in Japan for improvement of viraemia in patients with serogroup 1 (genotype I) chronic hepatitis C or compensated cirrhosis type C. Product information for both products will be updated to include this information.

- ▶ PMDA [Summary of investigation results and Revisions of precautions](#), 23 April 2015.

Fingolimod: progressive multifocal leukoencephalopathy

United Kingdom – The marketing authorization holder, in agreement with the EMA and Medicines and Healthcare Products Regulatory Agency (MHRA), has warned health professionals to be vigilant for the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with fingolimod. The medicine should be permanently discontinued if PML is confirmed.

This follows the first reported case, in February 2015, of PML in a multiple sclerosis patient taking fingolimod (Gilenya®) without previous treatment with natalizumab or other immunosuppressive medicines. PML was suspected on a routine brain MRI scan and confirmed by positive JC virus DNA in cerebrospinal

fluid using quantitative PCR. Fingolimod was stopped immediately upon confirmation of PML, and no signs or symptoms of PML had appeared at the time of communication.

PML is a rare and serious brain disease caused by reactivation of the JC virus in patients with a weakened immune system. The risk of PML with fingolimod is being evaluated further.

- ▶ [Drug Safety Update volume 8 issue 10 May 2015: 4](#).
[Letter to health professionals, 29 April 2015](#).

Pomalidomide: risks of cardiac failure, interstitial lung disease and hepatotoxicity

United Kingdom – The MHRA has issued new monitoring instructions for pomalidomide (Imnovid®), used to treat relapsed and refractory multiple myeloma. This follows an EMA review which identified cardiac failure and interstitial lung disease as common side effects of this medicine (affecting up to one in 10 patients), while serious liver damage was found to be uncommon (affecting up to one in 100 patients).

Cardiac failure occurred mostly in patients with cardiac disease or cardiac risk factors. Pomalidomide should be used with caution in these patients, and they should be monitored for signs and symptoms of heart failure.

Interstitial lung disease typically started within six months of starting treatment, but took as long as 18 months to appear in some cases. Health professionals should carefully assess patients with any new or worsening respiratory symptoms and stop pomalidomide during assessment. If interstitial lung disease is confirmed, it should be treated appropriately and pomalidomide should only be resumed

after a thorough evaluation of the benefits and risks.

Serious hepatotoxicity manifested mainly as acute hepatitis. Regular liver function monitoring is recommended during the first six months of treatment, when this risk appears to be highest. Insufficient data are available to support specific guidance on monitoring frequency.

► [MHRA Drug safety update, 20 May 2015.](#)

High-dose ibuprofen and dexibuprofen: cardiovascular risks

European Union – The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review confirming a small increase in the risk of cardiovascular problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (2400 mg or more per day). No increase in cardiovascular risk is seen with ibuprofen at doses up to 1200 mg per day.

The PRAC recommends to avoid doses of 2400 mg of ibuprofen per day or higher in patients with serious underlying heart or circulatory conditions and in those who have previously had a heart attack or stroke, and to assess a patient's cardiovascular risk factors before initiating long-term treatment with ibuprofen, particularly at high doses.

Data from laboratory studies further indicate that ibuprofen reduces the anti-clotting effects of aspirin. In clinical practice, occasional use of ibuprofen should not be a problem; however its long-term use may affect the benefits of low-dose aspirin in preventing heart attacks and strokes.

The above findings and recommendations also apply to dexibuprofen, with 1200 mg or more per day being considered a high dose.

Updated information will be included in product information for both medicines. (1)

Canada – A Health Canada safety review found that oral ibuprofen taken at doses of 2400 mg per day or more increases the risk of heart attack and stroke to levels similar to those seen with COX-2 inhibitors and diclofenac.

Prescription oral ibuprofen products in Canada have a maximum recommended daily dose of 2400 mg and are authorized to relieve the pain and inflammation of rheumatoid arthritis and osteoarthritis. The prescribing information will be updated to warn that doses of 2400 mg per day should not be used in patients who have a history of heart disease and stroke, or who have cardiovascular risk factors such as smoking, diabetes, high blood pressure, high blood cholesterol or a strong family history of cardiovascular disease.

The review found no evidence of an increased cardiovascular risk with over-the-counter ibuprofen products if they are used as directed, i.e. at a maximum daily dose of 1200 mg for no more than seven days. (2)

► (1) [EMA Press release, 13 April 2015.](#)

(2) [Health Canada Information update, 23 April 2015.](#)

ADHD medicines: risk of suicidal thoughts in certain patients

Canada – Following reports of suicide-related events in patients treated with Attention Deficit Hyperactivity Disorder (ADHD) medicines, Health Canada has revised the prescribing information for methylphenidate, amphetamines and guanfacin-containing ADHD products available on the Canadian market. For the ADHD drug atomoxetine (Strattera®)

the risk was already known and communicated in 2005.

Health Canada considers that although these medicines may contribute to suicidal thoughts in certain patients, the benefits of treatment continue to outweigh the risks. Health professionals should take psychiatric disorders into account when prescribing these medicines and should monitor each patient's psychological state during treatment.

► [Health Canada Information update, 30 March 2015.](#)

Varenicline: potential alcohol interaction and other effects

United States of America – The FDA is warning that the smoking cessation medicine varenicline (Chantix®) can change the way in which people react to alcohol. In addition, rare accounts of seizures in patients treated with varenicline have been reported. The FDA has approved changes to the product information to warn about these risks. Until patients know how varenicline affects their ability to tolerate alcohol, they should decrease the amount of alcohol they drink. Patients taking varenicline who have a seizure should stop the medicine and seek medical attention immediately.

Studies have been undertaken to investigate the risk of serious neuropsychiatric side effects of varenicline. The FDA will update the public when the outcomes become available.

► [FDA Drug safety communication, 9 March 2015.](#)

Rebamipide: adverse effects on the eye

Japan – The PMDA has reported that lacrimal duct obstruction and

dacryocystitis have been observed in Japan in patients treated with rebamipide (Mucosta®), an ophthalmic solution used to treat dry eyes. Product information will be updated to recommend patient monitoring, with discontinuation of the medicine and appropriate measures in case of any abnormalities.

► [PMDA Summary of investigation results and Revisions of precautions, 24 March 2015.](#)

Known risks

Ferumoxytol: strengthened warnings

United States of America – The FDA has strengthened an existing warning that serious, potentially fatal allergic reactions can occur with the intravenous iron replacement product ferumoxytol (Feraheme®). The product now carries a Boxed Warning about these serious risks, and is contraindicated in patients with a history of hypersensitivity to any intravenous iron product. In other patients it should only be used if the benefits outweigh the risks, and should be administered by infusion over at least 15 minutes with appropriate dilution. (1)

In July 2014 an EMA review of ferumoxytol had come to similar conclusions. (2)

► (1) [FDA Drug safety communication, 30 March 2015.](#)

(2) [EMA News, 11 July 2014.](#)

Triamcinolone acetonide: tendon rupture

Japan – The PMDA has reported that cases of tendon rupture have been observed in patients treated with injectable triamcinolone acetonide (Kenacort-A®) in

Japan. Product information in Japan will be updated to reflect this risk. (1)

These observations confirm the risk reflected in approved product information in Europe (2), which carry a warning that repeated injection of this medicine into inflamed tendons should be avoided as it has been shown to cause tendon rupture.

► (1) [PMDA Summary of investigation results and Revisions of precautions](#), 24 March 2015.

(2) Example: www.medicines.org.uk/emc/medicine/6392

Cyclophosphamide: rhabdomyolysis

Japan – Following reports of rhabdomyolysis in patients treated with the antineoplastic agent cyclophosphamide hydrate (Endoxan®) in Japan, the PMDA has recommended to update the product information for oral and injectable products. Signs of rhabdomyolysis include myalgia, feelings of weakness, increased creatine kinase (creatine phosphokinase), increased blood myoglobin, and increased urine myoglobin. If rhabdomyolysis occurs, the medicine should be stopped and appropriate measures taken. (1)

Approved product information for cyclophosphamide in the United Kingdom (2) includes rhabdomyolysis as a very rare adverse event.

► (1) [PMDA Summary of investigation results and Revisions of precautions](#), 24 March 2015.

(2) Example: www.medicines.org.uk/emc/medicine/29592

Panitumumab: Stevens-Johnson syndrome

Japan – Following reports of adverse events suggestive of Stevens–Johnson syndrome in patients treated with panitumumab (Vectibix®) in Japan and elsewhere, approved product information in Japan has been revised to include this risk. (1)

EMA-approved product information for panitumumab (2) lists Stevens-Johnson syndrome and toxic epidermal necrolysis rare adverse events, occurring in one of 1001-10000 patients treated.

► (1) [PMDA Summary of investigation results and Revisions of precautions](#), 24 March 2015.

(2) EMA. [Vectibix : EPAR - Product Information](#). Last updated 2 March 2015.

Pazopanib: retinal detachment

Japan – Following reports of retinal detachment in patients treated with the antineoplastic agent pazopanib (Votrient®) in Japan and elsewhere, the PMDA has recommended to add information about this adverse event to product information approved in Japan. If possible signs such as eye floaters, photopsia, visual field defect or reduced visual acuity are observed, ophthalmologic examination should be performed and appropriate measures taken. (1)

EMA-approved product information for pazopanib (2) includes this adverse effect as uncommon, occurring in one of 101-1000 patients treated.

► (1) [PMDA Summary of investigation results and Revisions of precautions](#), 24 March 2015.

(2) EMA. [Votrient : EPAR - Product Information](#). Last updated 9 February 2015.

Zoledronic acid: further measures to minimize risk of osteonecrosis of the jaw

European Union – The EMA has completed a periodic review of zoledronic acid (Aclasta®), one of the bisphosphonate medicines with a known risk of osteonecrosis of the jaw. Although the risk is very low, the EMA has recommended to update the product information and to introduce a patient reminder card to minimize this risk.

Patients should highlight any dental problems to their doctor before starting treatment, ensure good dental hygiene during treatment, inform their dentist that they are being treated with zoledronic acid, and contact the doctor and dentist if any problems with the mouth or teeth occur during treatment.

The risk also exists with other medicines used for osteoporosis and other conditions that affect the bones, such as other bisphosphonates and denosumab. Similar revisions will be considered as part of periodic reviews during 2015 and 2016.

► [EMA Press release, 27 March 2015.](#)

Duloxetine: neuroleptic malignant syndrome

Japan – The PMDA has warned about neuroleptic malignant syndrome having occurred in patients treated with duloxetine (Cymbalta®) in Japan, and has recommended to update the product information.

In 2006 the FDA had warned about the risk of a potentially life-threatening serotonin syndrome with serotonin noradrenaline reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors

(SSRIs), particularly with concomitant use of certain other nervous system drugs.

► (1) [PMDA Summary of investigation results and Revisions of precautions](#), 23 April 2015.

(2) [FDA Alert \[7/2006\]: Potentially Life-Threatening Serotonin Syndrome with Combined Use of SSRIs or SNRIs and Triptan Medications](#). Web page last updated 14 July 2013.

Unchanged recommendations

Rotavirus vaccine: benefits outweigh risks

Geneva – The Global Advisory Committee on Vaccine Safety has issued a statement to affirm that the safety profile of current rotavirus vaccines is acceptable, with the benefits of vaccination greatly exceeding risks.

This follows reported cases of intussusception in multiple countries for the two most widely used vaccines to prevent rotavirus gastroenteritis in young infants globally. The findings underscore the importance of close monitoring of infants and prompt medical care after vaccination. If recognized and treated early, intussusception generally has a good outcome and is rarely fatal.

The benefits of rotavirus vaccination are particularly important in resource-poor countries where rotavirus disease remains an important cause of mortality among young children.

► [WHO Essential medicines and health products. News, 11 May 2015.](#)

Natalizumab: no definite link with melanoma

Australia – The Therapeutic Goods Administration (TGA) has concluded its review of the immunosuppressant

medicine natalizumab (Tysabri®), and has found insufficient evidence of a definite link between this medicine and melanoma.

Natalizumab is used to treat patients with relapsing-remitting multiple sclerosis. Given the high incidence of melanoma in Australia, the TGA will continue to monitor this issue. Health professionals should ensure that any new or changed suspicious skin lesions in patients treated with natalizumab are promptly detected and investigated.

► [TGA Monitoring communication, 21 May 2015.](#)

Olanzapine: inconclusive findings after two deaths in 2013

United States of America – Following the deaths of two patients in 2013

after injection of appropriate doses of olanzapine pamoate (Zyprexa Relprevv®), the FDA's study to determine the causes has ended with inconclusive results. It is possible that the deaths were caused by rapid but delayed entry of the drug into the bloodstream following intramuscular injection, and that the high drug levels found in the two patients' blood occurred after death.

On the basis of all of the information reviewed, the FDA is not recommending any changes to the prescribing or use of olanzapine. Health care professionals are reminded to follow the requirements of the Risk Evaluation and Mitigation Strategy (REMS) for the product.

► [FDA Safety announcement, 23 March 2015.](#)

Safety reviews started

Medicine	Use	Concerns	Reviewing authority reference
Natalizumab (Tysabri®)	Treatment of multiple sclerosis	Possible need to revise advice on managing the risk of progressive multifocal leukoencephalopathy	► EMA News, 8 May 2015.
Inhaled corticosteroids	Treatment of chronic obstructive pulmonary disease (COPD)	Need to evaluate the known risk of pneumonia when these medicines are used for COPD	as above
Crizotinib (Xalkori®)	Treatment of certain types of lung cancer	Possible risk of cardiac failure	► PMDA risk communication, 8 May 2015.
Technetium (^{99m} Tc) injection (Clearbone®)	Scintigraphy	Possible risk of shock and anaphylaxis	as above

Data integrity concerns**GVK Biosciences: EMA confirms suspension of products over flawed studies**

European Union – The EMA has confirmed its January 2015 recommendation to suspend a number of medicines for which authorization in the EU was primarily based on clinical studies conducted at GVK Biosciences in Hyderabad, India. This is the outcome of a re-examination requested by marketing authorization holders for seven of the medicines concerned.

Around 700 pharmaceutical forms and strengths of medicines studied at the Hyderabad site remain recommended for suspension, while for around 300 others, including one included in the re-examination, sufficient supporting data from other sources had been provided. An updated list of medicines recommended for suspension is available on the EMA website. Some of these may remain on the market in countries where they are of critical importance to meet patients' needs; as decided by the national authorities of the respective EU Member State. For medicines that are considered critical, companies are given 12 months to submit additional data.

► [EMA Press release, 22 May 2015.](#)

Hospira S.P.A.: Health Canada restrict imports

Canada – Health Canada has restricted the importation of medicines from Hospira S.P.A. in Liscate, Italy, due to data integrity concerns raised by a trusted regulatory partner about the reliability of the laboratory data generated at this site.

The Canadian import licences for medicines from this facility are being amended to require independent third-party testing against the approved Canadian specifications prior to release of any medically necessary products. Products that are not on the medically necessary list will not be imported or released to the Canadian market until Health Canada is satisfied that the data integrity issues have been addressed. A list of affected products is available on the authority's web site, and updates will be provided through the online [Inspection Tracker](#).

► [Health Canada Advisory information update, 12 June 2015](#) (with subsequent updates).

Zhejiang Hisun Pharma, Polydrug Laboratories: Health Canada recommends voluntary quarantine

Canada – Health Canada has requested that Canadian importers voluntarily quarantine drug products with active pharmaceutical ingredients (APIs) manufactured or tested by Zhejiang Hisun Pharma Company Ltd., in Zhejiang, China (1) as well as those manufactured or tested by Polydrug Laboratories, in Ambarnath, Maharashtra, India (2), due to data integrity concerns.

No risk to health has been identified, and Health Canada is not requesting a recall of any products. The authority is providing updates on the situation through its [Inspection Tracker](#).

► (1) [Health Canada Advisory information, 16 June 2015.](#)

(2) [Health Canada Advisory information, 24 June 2015.](#)

Falsified product alert

Falsified meningitis vaccines circulating in West Africa

WHO has published a medical product alert relating to the confirmed circulation of falsified versions of meningitis vaccines in Niger. Following a report submitted to the WHO Surveillance and monitoring system for substandard and falsified medical products by the focal point within the Niger Regulatory Authority, increased vigilance is requested for the following lots/batches of vaccines and solvents.

- Product: **Mencevax ACW**
Batch number: **AMENA020AA**; manufacturing date: **12-2014**, expiry date: **11-2017**
The batch number is genuine but the manufacturing and expiry dates are false. The genuine version of this batch expired in 2011. The product contains 50 doses per vial.
- Product: **Mencevax ACWY**
Batch number: **AMEHA020AA**; manufacturing date: **12-2013**, expiry date: **11-2016**
The batch number, manufacturing date and expiry date for this product are false. This falsified product contains 50 doses per vial.
- Product: **Diluent for Mencevax**
Batch number: **A003B128AA**; manufacturing date: **02-2013**, expiry date: **01-2019**
The batch number, manufacturing date and expiry date for this diluent are false. This falsified product contains 50 doses of diluent.
- Product: **Menomune ACY-W135**; batch number: **UH 301AA**; expiry date: **29 APR 17**
The batch number is genuine but the expiry date is false. The genuine version of this batch of vaccine expired in 2014. This falsified product contains 10 doses per vial.
- Product: **Menomune ACYW-135**; batch number: **UH 301AA**; expiry date: **28 FEB 16**
The batch number is genuine but the expiry date is false. The genuine version of this batch of vaccine expired in 2014. This falsified product contains 10 doses per vial.
- Product: **Menomune ACYW-135**; batch number: **UH299AA**; expiry date: **28 FEB 16**
The batch number is genuine but the expiry date false. The genuine version of this batch of vaccine expired in 2014. This falsified product contains 10 doses per vial.
- Product: **Diluant for Menomune**; batch number: **UH 262 AA**; expiry date: **25 OCT 16**
The batch number is genuine but the expiry date false. The genuine version of this batch of diluant expires on 25 OCT 15. This falsified product contains sufficient solvent to reconstitute 10 doses of vaccine.
- Product: **Diluant for Menomune**; batch number: **D0953-1**; expiry date: **20-2017**
This is not a genuine batch number for a diluent for Menomune Vaccine. This falsified product contains sufficient solvent to reconstitute 10 doses of vaccine.

No serious adverse reactions linked to these batches of falsified vaccines have been reported at this stage. Genuine Mencevax is manufactured by GlaxoSmithKline (GSK), and genuine Menomune is manufactured by Sanofi Pasteur.

These falsified products have not yet been subject to laboratory analysis. The alert was issued on the basis of inconsistencies in the packaging material and confirmation from GSK and from Sanofi Pasteur that the batch numbers, manufacturing dates and expiry dates are inconsistent with the genuine product.

WHO advises increased vigilance within the supply chains of countries likely to be affected by these falsified products. It is necessary to ensure that vaccines are obtained from authentic and reliable sources. Ministry of Public Health / National medicines regulatory authorities are asked to immediately notify WHO via rapidalert@who.int if the above-mentioned batches are discovered in their countries.

▶ WHO Medical Product Alerts No. [2/2015, 22 May 2015](#) and [3/2015, 27 May 2015](#). (With photographs.)

WHO recognises the seriousness of the current meningitis outbreak in West Africa and the additional demand for meningitis vaccines. Further information concerning this outbreak is available at www.who.int/mediacentre/news/situation-assessments/meningitis-niger/en/.