Safety news

Safety warnings

Belladonna-containing teething products: risk to children
United States of America – An FDA laboratory analysis has found inconsistent amounts of belladonna in certain homoeopathic teething tablets, sometimes far exceeding the amount claimed on the label. The agency is warning that homoeopathic teething tablets containing the toxic substance belladonna pose a risk to infants and children, who may experience seizures, difficulty breathing, lethargy, excessive sleepiness, muscle weakness, skin flushing, constipation, difficulty urinating and agitation. The FDA urges consumers not to use these products. Homoeopathic teething products have not been evaluated or approved by the FDA for safety or effectiveness. In 2016 the FDA had warned consumers against the use of such products after receiving adverse event reports. (1)

Australia – Urgent testing conducted by the TGA in response to the safety concerns described above did not identify any quality issues. (2)

(2) TGA Update, 1 February 2017.

Hyoscine butylbromide injection: serious adverse events in patients with underlying heart disease
United Kingdom – The MHRA has warned health professionals that hyoscine butylbromide (also known as butylscopolamine) injection (Buscopan*) can cause serious adverse effects, including tachycardia, hypotension and anaphylaxis. These effects can result in fatal outcomes, especially in patients with underlying cardiac conditions such as heart failure, coronary heart disease, cardiac arrhythmia or hypertension.

Injectable hyoscine butylbromide is used to treat acute muscular spasm and to reduce spasm in certain diagnostic procedures. The MHRA recommends to use this medicine with caution in patients that have any of the above-mentioned conditions. These patients should be monitored, and it should be ensured that resuscitation equipment as well as personnel who are trained in its use are readily available. The MHRA has reminded health professionals that hyoscine butylbromide injection remains contraindicated in patients with tachycardia.

The warning was published following nine reported deaths of patients in the United Kingdom after administration of hyoscine butylbromide injection. The product information has been updated to include the new recommendations.


Lenalidomide: reactivation of hepatitis B virus
Japan – The PMDA has informed health professionals that cases of reactivation of hepatitis B virus (HBV) have been reported in patients treated with lenalidomide (Revlimide*) in Japan. HBV reactivation may occur in HBV carriers or in patients with a history of HBV infection.
Recommendations have been added to the product information to test patients for HBV before starting treatment, and to monitor them during treatment with lenalidomide by appropriate measures such as periodic hepatic function tests and monitoring of HBV markers.

► PMDA Summary of investigation results and MHLW Revisions of precautions, 10 January 2017.

Canagliflozin and other SLGT2 inhibitors: risk of amputations

European Union – The EMA has informed the public about a potential increased risk of lower limb amputations (mostly affecting the toes) in patients taking the sodium-glucose co-transporter 2 (SGLT2) inhibitors canagliflozin, dapagliflozin and empagliflozin. A review of these medicines was carried out by EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) in response to an increase in lower limb amputations observed in two ongoing clinical trials in patients treated with the canagliflozin. The mechanism by which canagliflozin may increase the risk of amputation is still unclear. An increased risk may also be associated with dapagliflozin and empagliflozin. Further data are expected from ongoing studies with these three SLGT2 inhibitors.

The product information for canagliflozin, dapagliflozin and empagliflozin will be updated based on available data; a warning of the potential increased risk of toe amputation highlighting the importance of routine preventative foot care will be included. For canagliflozin the risk of lower limb amputation will be listed as an uncommon side effect. If patients on canagliflozin develop significant foot complications such as infection or skin ulcers, treatment discontinuation should be considered.


Gadolinium-based contrast agents: accumulation in the brain

Canada – Health Canada has conducted a safety review of gadolinium-based contrast agents (GBCAs) due to growing scientific evidence that gadolinium may accumulate in the brain following multiple contrast-enhanced magnetic resonance imaging (MRI) scans. The evidence suggests that gadolinium accumulation in the brain is higher with the use of linear agents than with the use of macrocyclic agents.

Although no health consequences have been identified with gadolinium accumulation in the brain, Health Canada is requiring updates to the product information for GBCAs, advising health professionals to limit the use of these contrast agents to situations where they are considered necessary, to use the lowest effective dose, and to assess the benefits and potential risks to individual patients before administering repeated doses. (1)

Reviews are also ongoing in the United States (2) and the European Union (3).

► (1) Health Canada Advisory, 5 January 2017
(2) FDA Drug safety announcement, 27 July 2015.
(3) EMA. Article 31 Review started, 18 March 2016.

Restrictions

Dienogest and ethinylestradiol: can be used for acne as a last resort

European Union – The EMA has recommended that combination products containing dienogest and ethinylestradiol
can be used for the treatment of moderate acne, but only if suitable local therapies or oral antibiotic treatment have failed, and only in women who also choose to use oral contraception.

Like all combined hormonal contraceptives, dienogest and ethinyl-estradiol is associated with a risk of venous thromboembolism. While the risk is generally considered as low, available data are insufficient to quantify it for this specific combination. EMA recommends to consider each individual woman’s risk factors for venous thromboembolism before prescribing dienogest and ethinylestradiol for acne, and to reassess the need for continued treatment 3–6 months after starting treatment and periodically thereafter.


Known risks

Chlorhexidine gluconate: serious allergic reactions

United States of America – The FDA has warned health professionals that rare but serious allergic reactions, including anaphylaxis, have been reported with the widely used topical antiseptic products containing chlorhexidine gluconate. The number of reports has increased in past years.

Prescription-only mouthwashes and oral chips containing chlorhexidine gluconate approved in the U.S. include a warning about the risk of serious allergic reactions in the product information. Such a warning is now also required for over-the-counter (OTC) products containing chlorhexidine gluconate.

► FDA Drug safety announcement, 2 February 2017.

Fluoroquinolones: severe, disabling side effects

Canada – Healthcare professionals have been reminded about the potential for disabling and persistent serious adverse events with oral and injectable fluoroquinolone antibiotics. Health Canada is working with manufacturers to strengthen the prescribing information for these medicines.

The reminder follows rare reports of adverse events, including tendinopathy, peripheral neuropathy and central nervous system disorders, following systemic use of fluoroquinolones in Canada. In 2016, the U.S. FDA had restricted the use of fluoroquinolones to certain serious infections because of this risk. The EMA has started a review of this known risk associated with quinolones and fluoroquinolones (see under “Reviews started”).


Interferon beta-1b: thrombotic damage in small blood vessels

Japan – The PMDA has informed health professionals about reports of thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) in patients treated with interferon beta-1b in Japan and in other countries. Patients should be monitored through periodic blood tests such as platelet tests or red blood cell counts, and/or renal function tests as appropriate. The product information has been updated accordingly. (1)

A warning about thrombotic microangiopathy (TMA), manifesting as TTP or HUS, was added to the EMA-approved product information for interferon beta-1b products in July 2014, together with recommendations for monitoring of
early symptoms, prompt treatment and discontinuation of interferon beta as soon as the reaction is diagnosed.\(^{(2)}\) The FDA-approved product information for interferon beta-1B was updated in December 2015 to include a warning about TMA.\(^{(3)}\)

---

**Menthol-containing topical analgesics: serious skin burns**

Canada – A Health Canada review has found a risk of serious skin burns with the use of certain OTC topical pain relievers containing menthol. Available data were not sufficient to determine whether the risk is linked to any specific brand, formulation or menthol concentration, or any ingredient other than menthol. The review also looked at the ingredients methyl salicylate and capsaicin, and did not find sufficient evidence to confirm the same risk with either of these ingredients alone.

A warning about the risk of burns is already included in the product information for certain products. Health Canada will publish an updated labelling standard for all menthol-containing topical analgesics.


---

**Tramadol: risk of serious breathing problems**

Canada – Based on the findings of a Health Canada safety review, the product information for tramadol-containing products has been updated to further highlight the risk of serious breathing problems. A warning has also been added that this risk is increased in patients who are “ultra-rapid metabolizers” of tramadol. The opioid medicine tramadol is approved in Canada to treat moderate to moderately severe pain in adults. Health professionals have been reminded that tramadol is not approved in Canada for use in patients under 18 years of age.\(^{(1)}\)

A similar review was initiated in the United States in 2015.\(^{(2)}\)


► FDA Drug safety communication, 21 September 2015.

---

**Varenicline and bupropion: risks said to be lower than expected**

United States of America – Based on the findings of a large clinical trial the FDA has determined that the benefits of varenicline and bupropion in helping people to stop smoking outweigh their risks of serious adverse effects on mood, behaviour or thinking. The results showed that these risks were present, especially in people having being treated for mental illnesses, but that in most patients they did not have serious consequences such as hospitalization. The warning sections of the medicines are being updated accordingly. Products containing bupropion, which is an antidepressant, will continue to carry a “Boxed Warning” about suicidality in patients treated with antidepressant medicines.

► FDA Drug safety communication, 16 December 2016.
Herbal products

Toxic alkaloids in plant-based products
Switzerland – Swissmedic has required marketing authorization holders to conduct risk evaluation and assays in order to mitigate the risk of toxic pyrrolizidine alkaloids contained in plant-based foods, teas and medicinal products. The toxic substances enter the products through weeds that are harvested with the plants.

Hundreds of structurally different pyrrolizidine alkaloids occurring in several thousand different plant species have been identified, and their toxic effect has been known for a long time. Many plant-based foods and medicinal plants are affected by the weed problem. It has been shown that measures going beyond the existing Good Agricultural and Collection Practice (GACP) are needed to ensure the quality and safety of these products. In May 2016 the EMA had published a statement with

Reviews started

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Use</th>
<th>Concerns</th>
<th>Reviewing authority reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain anaesthetics and sedatives</td>
<td>General anaesthesia and sedation</td>
<td>Lengthy use in young children or pregnant women may have potential negative effects on the development of children's brains</td>
<td>► Health Canada Advisory, 22 December 2016. See also: FDA Drug safety communication, 14 December 2016</td>
</tr>
<tr>
<td>Selexipag (Uptravi®)</td>
<td>Treatment of pulmonary arterial hypertension</td>
<td>Deaths of 5 patients taking the medicine in France. Based on a preliminary review of available data, EMA advised that the product may continue to be used both in existing and new patients, provided that the recommendations and precautions in the current prescribing information are followed carefully.</td>
<td>► EMA Press release, 10 February 2017. (As updated on 14 February 2017).</td>
</tr>
<tr>
<td>Systemic and inhaled quinolones and fluoroquinolones</td>
<td>Treatment of infections</td>
<td>Persistent serious side effects mainly affecting muscles, joints and the nervous system.</td>
<td>► EMA. Article 31 Referral. Quinolone- and fluoroquinolone-containing medicinal products, 10 February 2017.</td>
</tr>
</tbody>
</table>
recommendations for risk management and quality control.
► Swissmedic announcement, 6 February 2017.

EMA. Public statement on contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids; Transitional recommendations for risk management and quality control. 31 May 2016.

Non-compliance with good practices

Micro Therapeutic Research Labs Pvt Ltd, India
European Union – The EMA has started a review of medicines for which studies have been conducted by Micro Therapeutic Research Labs at its Chennai site or its Coimbatore site in India. This follows a good clinical practice (GCP) inspection in February 2016, which raised concerns about the study data used to support a number of marketing authorization applications in the EU. Several national medicines regulatory agencies have requested EMA to assess the impact of the findings on medicines currently authorized or under evaluation in the EU on the basis of studies performed at the two sites.
► EMA. Article 31 Review started, 16 December 2017.

Chongqing Pharma Research Institute, China (and 11 others)
United States of America – Following an inspection conducted in May 2016, the FDA has warned the active pharmaceutical ingredient manufacturer Chongqing Pharma Research Institute Co. Ltd over data integrity issues. Audit trails from laboratory equipment used to perform high performance liquid chromatography and gas chromatography analyses showed that entire chromatographic sequences and individual injections had been deleted. The FDA investigator was told that it is laboratory practice to perform more injections than required by procedure, and then to delete any undesirable result. Analyses were repeated – without any scientific justification, investigation or documentation of original out-of-specification or otherwise undesirable test results – until acceptable results were obtained. These manipulated test results and incomplete records were used to support batch release decisions.

The FDA has requested the company to respond within 15 days providing details of remedial action.
► FDA Warning letter No. 320-17-24, 14 February 2017.

Since the beginning of 2017 the FDAs Center for Drug Evaluation and Research has issued a total of 12 warning letters to foreign companies, as published on the FDA website as of 8 March. The warnings were issued to five companies based in China, three in India, and two each in Japan and Europe. FDA warning letters are publicly available at https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/.

FDA Warning letter No. 320-17-24, 14 February 2017.

Since the beginning of 2017 the FDAs Center for Drug Evaluation and Research has issued a total of 12 warning letters to foreign companies, as published on the FDA website as of 8 March. The warnings were issued to five companies based in China, three in India, and two each in Japan and Europe. FDA warning letters are publicly available at https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/.