

DRUG INFORMATION AND PHARMACOVIGILANCE NEWS

European Medicines Agency (EMA): Risk of hyperammonemic encephalopathy associated with regorafenib use

Source: <https://www.who.int/publications/b/81054>
 Nguyen Mai Hoa, Bui Thi Phuong Thao

The Pharmacovigilance Risk Assessment Committee (PRAC) identified cases of hyperammonemic encephalopathy in patients treated with regorafenib, including fatal cases. Therefore, PRAC has requested that the marketing authorisation holder update the product information for regorafenib to include a warning regarding the risk of hyperammonemic encephalopathy.

Recommendations for healthcare professionals:

- Measure blood ammonia levels in patients who develop unexplained somnolence or changes in mental status during treatment with regorafenib.
- Consider permanent discontinuation of regorafenib if hyperammonemic encephalopathy attributable to regorafenib is confirmed.

Therapeutic Goods Administration (TGA): Risk of overdose associated with the use of topical creams containing prilocaine and lidocaine in young children

Source: <https://www.tga.gov.au/safety/safety-monitoring-and-information/safety-alerts/risk-overdose-babies-when-using-prilocainelidocaine-cream-empla-and-generic-brands>

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TGA investigated two cases of serious adverse events in young children who had the application of topical anesthetic creams containing prilocaine and lidocaine. Both cases were likely to have involved overdose, resulting from the use of excessive amounts of prilocaine/lidocaine cream for local anesthesia prior to minor surgical procedures.

Overdose of prilocaine/lidocaine may lead to serious adverse effects, including methemoglobinemia, a condition that impairs the oxygen-carrying capacity of red blood cells. In severe cases, methemoglobinemia can result in seizures or death. Clinical manifestations of methemoglobinemia may include headache, dizziness, dyspnea, nausea, impaired coordination, pallor, or cyanosis. In addition, other serious complications such as seizures and cardiac arrhythmias may occur.

The TGA has worked with manufacturers of topical products containing prilocaine/lidocaine to ensure that the risk of overdose is adequately reflected in the product information.

Recommendations for healthcare professionals:

- Provide careful instructions to parents and caregivers on the use of any topical anesthetic products, particularly when used in neonates and young children.
- Emphasize to parents and caregivers the importance of strict adherence to the recommended dose and duration of use to prevent the risk of overdose.

French National Agency for the Safety of Medicines and Health Products (ANSM): Warning on the risk of botulism associated with improper cosmetic botulinum toxin injections

Source: <https://ansm.sante.fr/actualites/injections-illegales-de-toxine-botulinique-ne-mettez-pas-en-danger-votre-sante>
 Nguyen Mai Hoa, Bui Thi Phuong Thao

ANSM observed several cases of severe botulism following illegal cosmetic botulinum toxin injections. In these cases, botulinum toxin was administered by unlicensed individuals, resulting in serious health consequences for clients.

Botulinum toxin is an injectable medicinal product used in aesthetic medicine to temporarily reduce facial wrinkles. However, it is a potent neurotoxin and is also indicated for the treatment of various neurological and neuromuscular disorders. Consequently, inappropriate use, incorrect dosing, or the use of products of unknown origin may lead to severe neurotoxic effects (botulism), which can be life-threatening or fatal. Cosmetic botulinum toxin injections must be performed by physicians or appropriately trained and certified healthcare professionals (such as specialists in plastic, reconstructive and aesthetic surgery; dermatology; head and neck surgery; maxillofacial surgery; and ophthalmology), in licensed healthcare facilities, using products that are authorised for use and whose safety and efficacy have been established. Injections performed outside

authorised medical settings carry substantial risks, including infection, skin necrosis, allergic reactions, and even death.

Botulism may cause acute neurotoxic manifestations, with symptoms including blurred or double vision, abnormal ptosis; marked muscle weakness, difficulty walking, and progressive symmetrical descending paralysis with preserved consciousness; dysarthria or dysphagia (choking); and respiratory distress. Severe cases require hospitalisation, potentially intensive care management, and may result in death. Since the most recent warning, ANSM recorded three additional serious adverse events associated with illegal cosmetic botulinum toxin injections in France.

EMA: Risk of circulatory shock associated with the use of co-trimoxazole (sulfamethoxazole/trimethoprim)

Source: <https://www.who.int/publications/>
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Cases of circulatory shock were reported with the use of co-trimoxazole, often accompanied by fever and unresponsive to standard management for hypersensitivity reactions. The majority of these cases were reported in immunocompromised patients.

Following a review of the available evidence from the literature and the EudraVigilance database, the PRAC has recommended the inclusion of circulatory shock, with an unknown

frequency, as an adverse reaction in the product information of medicines containing co-trimoxazole (sulfamethoxazole and trimethoprim). In addition, patients are advised to seek immediate medical attention if they develop signs of circulatory shock, such as fever, hypotension, or tachycardia, after using co-trimoxazole.

Health Canada: Safety review on the risk of liver injury associated with oral turmeric and curcumin-containing products

*Source: <https://dhpp.hpfb-dgpsa.ca/>
Nguyen Mai Hoa, Bui Thi Phuong Thao*

Health Canada conducted a safety review to assess the risk of hepatotoxicity associated with the use of oral products containing turmeric or curcuminoids. This safety review was initiated following the identification of rare case reports of serious liver injury after the use of turmeric- and curcumin-containing products from the scientific literature and reports from other regulatory authorities worldwide. Products containing turmeric and curcuminoids are authorised in Canada for the relief of joint pain and inflammation and for their antioxidant effects. Turmeric and curcuminoids may also be used in herbal products to support digestion or liver health, or in traditional Chinese medicine formulations. Most oral products containing turmeric or curcuminoids are not authorised for use in children under 18 years of age and

are not recommended for patients with biliary disorders (conditions involving the gallbladder and/or bile ducts).

Health Canada's assessment was based on all available information from regulatory authorities worldwide, as well as a review of the Canada Vigilance database, the World Health Organization (WHO) global database of adverse drug reactions, and published scientific literature. Health Canada identified 12 cases of liver injury following the use of products containing turmeric or curcumin. In all 12 cases, clinical information was incomplete and/or confounding factors were present, such as underlying medical conditions and the concomitant use of other medications or products known to affect the liver. Nevertheless, a causal relationship with the use of turmeric- or curcumin-containing products could not be excluded.

Health Canada analysed more than 60 international reports of liver injury associated with oral use of turmeric or curcuminoids, including reports from the WHO adverse drug reaction database and published literature. Among these, three fatal cases were reported, including two cases of liver injury assessed as being related to the use of oral turmeric- or curcumin-containing products. Although liver injury is very rare and the exact mechanism remains unclear, these case reports suggest a potential association with turmeric or curcuminoids.

Regulatory authorities in Australia, Italy, and France had also implemented risk management measures, such as updating the product information of oral turmeric- or

curcuminoid-containing products to include warnings about the risk of liver injury and appropriate advice for consumers.

Available evidence suggests that the risk of liver injury associated with turmeric- or curcuminoid-containing products does not appear to be dose- or duration-dependent and is difficult to predict due to incompletely defined risk factors. In most cases, liver injury was reversible following discontinuation of the product.

Health Canada's conclusions:

Health Canada has determined that there is a possible association between the oral use of turmeric or curcuminoids and the risk of liver injury. Health Canada recommends that manufacturers update product labels to include warnings regarding the risk of liver injury for products containing turmeric and curcuminoids, specifically:

- Warnings about the signs and symptoms of liver injury, including yellowing of the eyes or skin, dark urine, nausea, vomiting, and abdominal pain.
- Advice for consumers to consult a healthcare professional before using turmeric- or curcumin-containing products if they have existing liver disease or are taking multiple medications that may affect the liver, and to discontinue use if symptoms of liver injury occur.

Health Canada will also actively communicate this risk to healthcare professionals and consumers and will continue to monitor safety information related to turmeric- and curcuminoid-containing products, as well as all products

on the Canadian market, to detect and assess new safety issues.

Health Canada: Risk of serious liver injury associated with the use of Bruton's tyrosine kinase (BTK) inhibitors

*Source: <https://dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR1762956369249>
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Bruton's tyrosine kinase (BTK) inhibitors are a class of medicines indicated for the treatment of various hematological malignancies. In addition, ibrutinib can be used to treat chronic graft-versus-host disease (a complication following bone marrow transplantation) when other treatment options have failed and additional therapy is required. All BTK inhibitors are administered orally. Liver injury, including drug-induced liver injury (DILI), is a rare adverse reaction but may be life-threatening; elevated liver enzymes may progress to liver failure or necessitate liver transplantation.

Health Canada conducted a safety review to assess the risk of serious hepatotoxicity associated with the use of Bruton's tyrosine kinase (BTK) inhibitors. This safety review was initiated after Health Canada received information from manufacturers regarding new risk management measures implemented in other countries. Prior to the initiation of this review, the manufacturer of Imbruvica (ibrutinib) had already updated the product

information to include the risk of serious liver injury. Accordingly, Health Canada's review aimed to determine whether this risk applies to all drugs within the BTK inhibitor class and whether a class-wide update of product labelling is warranted.

Health Canada's assessment was based on data submitted by manufacturers and by an international regulatory authority, as well as information from the Canada Vigilance database and other available published literature. Health Canada identified 11 cases (1 domestic case and 10 international cases) of serious liver injury following the use of zanubrutinib or acalabrutinib, including two cases reported in the published literature. All 11 events were assessed as having a possible causal relationship with BTK inhibitors. Health Canada also reviewed 20 articles published in peer-reviewed scientific journals. Although certain limitations remained, such as the inability to fully exclude confounding factors (other potential

causes of hepatotoxicity) and incomplete clinical information, these data further strengthened the evidence supporting an association between all BTK inhibitors and the risk of serious liver injury.

Health Canada's conclusions:

- Health Canada has determined that there is an association between the use of BTK inhibitors and the risk of serious liver injury.
- Health Canada has worked with manufacturers to update product information for marketed BTK inhibitors to include warnings regarding the risk of serious liver injury.
- Health Canada will also enhance communication of this risk to healthcare professionals through the *Health Product InfoWatch* bulletin.
- Health Canada encourages patients and healthcare professionals to report any adverse reactions experienced during the use of BTK inhibitors or other medicines.

Correction: Molecular dynamics simulation of histone deacetylase enzyme with zinc ion and application

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Due to an oversight by the authors during the drafting process, the Editorial Board hereby corrects the article: **Molecular dynamics simulation of histone deacetylase enzyme with zinc ion and application**, This article was published in Volume 20, 2024, pages 49-57 with the added content in the section:

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The authors apologize for this error.

Sincerely.