Drug News
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Issue Number 188

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in June 2025 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).

Safety Update

Australia: Medicines containing GLP-1 and dual GIP/GLP-1 receptor agonists

On 3 June 2025, the Therapeutic Goods Administration (TGA) announced new warnings added of risks during anaesthesia or deep sedation.

Summary
Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RAs are relatively new and high-profile classes of medicines that are used to treat type 2 diabetes mellitus (T2DM) and/or obesity.

The GLP-1 RAs currently marketed in Australia include:

- Ozempic (semaglutide), Trulicity (dulaglutide) and Victoza (liraglutide), which are approved for the management of adults with T2DM.
- Saxenda (liraglutide) and Wegovy (semaglutide), which are approved for chronic weight management in patients who are obese or overweight.

The dual GIP/GLP-1 RA currently marketed in Australia:

- Mounjaro (tirzepatide) is approved for both T2DM and chronic weight management.

There is a known potential for all medicines in these classes to delay passage of food through the stomach (gastric emptying).

This poses a potential risk for patients during general anaesthesia or deep sedation as the usual fasting period beforehand may not be sufficient to empty the stomach.

TGA has required updates to Product Information (PI) and Consumer Medicine Information (CMI) documents for all these medicines with a warning about the risk of accidentally inhaling stomach contents during general anaesthesia or deep sedation.

Trulicity and Ozempic are available on the PBS (authority streamlined).

What health professionals should do
Be alert to the class-wide warning being added to the PIs for these medicines about the risk of pulmonary aspiration during general anaesthesia or deep sedation.

Advise patients of the risk and to alert health professionals, including anaesthetists, that they are taking one of these medicines before a surgical procedure to ensure appropriate management.

Anaesthetists should:

- be particularly alert that residual gastric contents may remain despite preoperative fasting in patients taking these medicines
- ask patients whether they are taking one of these medicines
- consider the risk of aspiration in patients taking these medicines within the preoperative risk assessment, so it can be managed appropriately.

Information for consumers
Patients are advised to tell health professionals, including anaesthetists, that they are taking one of these medicines before a surgery or other procedures.

Background
In 2023, the TGA conducted an independent assessment following sponsor notification of a safety signal from the US Food and Drug Administration (FDA) regarding aspiration during general anaesthesia (GA) and deep sedation for

these medicines.

TGA approved updates to the PIs of all 3 GLP-1 receptor agonists on the ARTG (dulaglutide, liraglutide and semaglutide; under 5 trade names) and one dual GIP/GLP-1 receptor agonist (tirzepatide) to include a precaution in section 4.4 for aspiration during GA and deep sedation.

Delayed gastric emptying, which is a risk factor for aspiration, was already a recognised effect described in the PI of all these medicines.

Adverse events reported to TGA
A search of TGA's publicly available Database of Adverse Event Notification (DAEN) on 14 May 2025 for the GLP-1 and dual GIP/GLP-1 receptor agonists identified 7 cases for aspiration and 1 case of pneumonia aspiration for semaglutide, 1 case of aspiration and 1 case of pneumonia aspiration for liraglutide and 1 case of pneumonia aspiration for dulaglutide. All cases were reported with a single suspected medicine.

Changes to the PI
The following warning has been added to the PIs for Trulicity (dulaglutide), Victoza (liraglutide), Saxenda (liraglutide), Ozempic (semaglutide), Wegovy (semaglutide), and Mounjaro (tirzepatide):

> 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
>
> Aspiration in association with general anaesthesia or deep sedation
>
> Cases of pulmonary aspiration have been reported in patients receiving GLP-1 RAs undergoing general anaesthesia (GA) or deep sedation despite reported adherence to preoperative fasting recommendations. Therefore, the increased risk of residual gastric content because of delayed gastric emptying should be considered prior to performing procedures with GA or deep sedation.

In Hong Kong, there are registered pharmaceutical products containing GLP-1 and dual GIP/GLP-1 receptor agonists including dulaglutide (4 products), exenatide (1 product), liraglutide (5 products), lixisenatide (2 products), semaglutide (11 products), and tirzepatide (6 products). All products are prescription-only medicines. As of the end of June 2025, the Department of Health (DH) had received 10 cases of adverse drug reactions with regard to semaglutide, of which 4 were related to pulmonary aspiration. The DH had also received adverse drug reactions with regard to dulaglutide (5 cases), exenatide (2 cases), liraglutide (1 case) and lixisenatide (1 case), but these cases were not related to aspiration or pulmonary aspiration. The DH had not received any case of adverse drug reaction related to tirzepatide. Related news was previously issued by the European Medicines Agency and the United Kingdom Medicines and Healthcare products Regulatory Agency, and was reported in the Drug News Issue No. 177 and 183. The DH issued letters to inform local healthcare professionals to draw their attention on 15 July 2024. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board of Hong Kong

European Union: PRAC reviewing risk of encephalitis with varicella vaccines

On 6 June 2025, the European Medicines Agency (EMA) announced that its safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), is reviewing the known risk of encephalitis (inflammation of the brain) with two varicella (chickenpox) vaccines, Varilrix and Varivax, following a report of a fatal outcome after vaccination with Varilrix.

In the European Union (EU), Varilrix and Varivax are authorised for vaccination of adults and children from 12 months of age, and in certain populations from 9 months of age, against chickenpox. They contain live attenuated (weakened) varicella virus.

Varicella is caused by the varicella-zoster virus, which also causes shingles (herpes zoster). Varicella mainly affects children aged 2-8 years where it is usually a mild disease and children recover quickly. In some cases, varicella can cause complications including bacterial infection of the skin or blood, pneumonia (infection and inflammation of the lungs) and encephalitis. Encephalitis can also be caused by other viral or bacterial infections. While most people with encephalitis recover, the condition can be life-threatening.

This review was initiated by the PRAC following a case report in Poland of a child who developed encephalitis a few days after receiving the Varilrix vaccine. The patient died of the consequences of encephalitis several days later. As a precaution, the Polish medicines agency has suspended the distribution of vaccines from the batch in question.

These vaccines are widely used across the EU, and encephalitis is listed as a side effect in their product information based on rare reports during post-marketing surveillance.

The committee will now assess all available evidence to better understand the risk of encephalitis and to determine if any regulatory action is necessary.

In Hong Kong, Varilrix Vaccine For Inj (HK-41798) and Varivax Vaccine (HK-39958) are pharmaceutical products registered by GlaxoSmithKline Limited and Merck Sharp & Dohme (Asia) Ltd respectively, and both products are prescription-only medicines. As of the end of June 2025, the Department of Health (DH) had received 1 case of adverse drug reaction related to Varilrix, but it was not related to encephalitis. The DH had not received any cases of adverse drug reactions related to Varivax. In light of the above EMA's announcement, the DH will remain vigilant on the review started by EMA and any safety update of the drugs issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

European Union: PRAC concludes eye condition NAION is a very rare side effect of semaglutide medicines Ozempic, Rybelsus and Wegovy

On 6 June 2025, the European Medicines Agency (EMA) announced that its safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), has concluded its review of medicines containing semaglutide following concerns regarding a possible increased risk of developing non-arteritic anterior ischemic optic neuropathy (NAION), an eye condition that may cause loss of vision. Semaglutide, a GLP-1 receptor agonist, is the active substance in certain medicines used in the treatment of diabetes and obesity (namely Ozempic, Rybelsus and Wegovy).

After reviewing all available data on NAION with semaglutide, including data from non-clinical studies, clinical trials, post-marketing surveillance and the medical literature, PRAC has concluded that NAION is a very rare side effect of semaglutide (meaning it may affect up to 1 in 10,000 people taking semaglutide).

Results from several large epidemiological studies suggest that exposure to semaglutide in adults with type 2 diabetes is associated with an approximately two-fold increase in the risk of developing NAION compared with people not taking the medicine. This corresponds to approximately one additional case of NAION per 10,000 person-years of treatment; one person-year corresponds to one person taking semaglutide for one year. Data from clinical trials also point to a slightly higher risk of developing the condition in people taking semaglutide, compared with people taking placebo (a dummy treatment).

EMA has therefore recommended that the product information for semaglutide medicines is updated to include NAION as a side effect with a frequency of 'very rare'. If patients experience a sudden loss of vision or rapidly worsening eyesight during treatment with semaglutide, they should contact their doctor without delay. If NAION is confirmed, treatment with semaglutide should be stopped.

More about the medicines
Semaglutide, a GLP-1 receptor agonist, is the active substance in certain medicines used in the treatment of diabetes and obesity (namely Ozempic, Rybelsus and Wegovy). Semaglutide acts in the same way as GLP-1 (a natural hormone in the body) by increasing the amount of insulin that the pancreas releases in response to food. This helps with the control of blood glucose levels. Semaglutide also regulates appetite by increasing a person's feelings of fullness, while reducing their food intake, hunger and cravings.

More about the procedure
The potential association between exposure to semaglutide and NAION (non-arteritic anterior ischemic optic neuropathy) was evaluated as part of a post-authorisation measure (LEG) resulting from a PSUR assessment.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations.

The PRAC recommendations will now be sent to

the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt the Agency's opinion. The CHMP opinion will then be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course.

In Hong Kong, there are 11 registered pharmaceutical products containing semaglutide. All products are prescription-only medicines. As of the end of June 2025, the Department of Health (DH) had received 10 cases of adverse drug reaction related to semaglutide, but these cases were not related to NAION. Related news was previously issued by the EMA, and was reported in the Drug News Issue No. 183. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 9 June 2025, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board of Hong Kong.

The United Kingdom: Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell): updated safety and educational materials to support patient discussion on reproductive risks

On 10 June 2025, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that updated safety and educational materials are now available to support the implementation of the regulatory measures announced in the November 2023 National Patient Safety Alert and the September 2024 Drug Safety Update. They also include previous updates to product information on the risk of low birth weight in children exposed to valproate during pregnancy.

Advice for Healthcare Professionals:

- updated safety and educational materials are now available to support healthcare professionals and patients to implement the existing regulatory requirements
- the updates reflect:
  - precautionary advice on the potential risk of neurodevelopmental disorders in children fathered by men taking valproate around the time of conception
  - a risk of lower weight at birth for the gestational age in children exposed to valproate during pregnancy
- healthcare professionals should review the new materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing valproate

As a reminder

- valproate must not be started in new patients (male or female) younger than 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply
- valproate must not be prescribed to any woman or girl able to have children unless the conditions of the Pregnancy Prevention Programme (PPP) are followed
- as a precaution, recommend that male patients use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate. For further information, see the September 2024 Drug Safety Update

Advice for Healthcare Professionals to Provide to Patients:

- do not stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may worsen without treatment
- women and girls who are able to have children and who are taking valproate must follow the conditions of the Pregnancy Prevention Programme
- as a precaution it is recommended that male patients taking valproate should use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate
- if you are on valproate, please attend any offered appointments to discuss your treatment plan and talk to a healthcare professional if you are concerned. If you wish to discuss family planning, please contact a healthcare professional
- consult the Patient Information Leaflet and Patient Guide for men or Patient Guide for women for information about the risks of valproate – also the MHRA information page for information resources

Background
In September 2024, precautionary advice was communicated in Drug Safety Update on a potential risk of neurodevelopmental disorders in children fathered by men taking valproate around the time of conception. In February 2025, a Drug Safety Update communicated that review by two specialists remains in place for all patients initiating valproate under 55 years of age but the Commission on Human Medicines had advised that it will not be required for men (or males) currently taking valproate. Three infographics were published to clarify in which situations review by two specialists may be required:

- for female patients under 55 years old
- for male patients under 55 years old
- for male and female patients 55 years and older

Risk of lower weight at birth for gestational age
Product information has been updated to reflect epidemiological studies (please see references in 'Additional Information' section in the website in MHRA) which have reported a decrease in mean birth weight, and a higher risk of being born with a low birth weight (<2500 grams) or small for gestational age (defined as birth weight below the 10th percentile corrected for their gestational age, stratified by gender) for children exposed to valproate in utero in comparison to unexposed or lamotrigine-exposed children.

Updated safety and educational materials
Safety and educational materials have been updated in line with the current regulatory position and to reflect feedback from stakeholders.

The following new or updated safety and educational materials are now available online:

- Annual Risk Acknowledgement Form for female patients
- Risk Acknowledgement Form for male patients starting valproate
- Patient guide for women
- Patient guide for men
- Patient card
- Booklet for healthcare professionals
- Valproate dispensary poster

In Hong Kong, there are 10 registered pharmaceutical products containing valproate. All products are prescription-only medicines. As of the end of June 2025, the Department of Health (DH) had received 17 cases of adverse drug reaction with regard to valproate, of which 2 cases were reported as congenital malformations following valproate exposure in utero, and these cases were not related to neurodevelopmental disorders in children after paternal exposure to valproate or low birth weight for children exposed to valproate in utero. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 21, with the latest update reported in the Drug News Issue No. 185. The DH issued letters to inform local healthcare professionals to draw their attention on 4 July 2011, 7 May 2013, 13 October 2014, 12 February 2018, 13 December 2022 and 22 March 2023.

The Registration Committee of the Pharmacy and Poisons Board of Hong Kong discussed the matter related to the risks in pregnancy associated with the use of valproate in September 2011, December 2014, December 2018 and June 2019. Currently, the package insert or sales pack label of locally registered valproate-containing products should include safety information on the risk of malformations and impaired cognitive development in children exposed to valproate during pregnancy, and contraindications, e.g. in women of childbearing potential unless pregnancy preventive measures have been implemented, etc. The certificate holders of locally registered valproate-containing products are also required to implement risk minimisation measures, e.g. patient information leaflet should be provided, etc.

In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 11 June 2025, and the matter will be further discussed by the Registration Committee of the Pharmacy and Poisons Board of Hong Kong.

The United States: FDA approves required updated warning in labeling of mRNA COVID-19 Vaccines regarding myocarditis and pericarditis following vaccination

On 25 June 2025, the United States Food and Drug Administration (FDA) announced that it has required and approved updates to the Prescribing Information for Comirnaty (COVID-19 Vaccine, mRNA) manufactured by Pfizer Inc. and Spikevax (COVID-19 Vaccine, mRNA) manufactured by ModernaTX, Inc. to include new safety information about the risks of myocarditis and pericarditis following administration of mRNA COVID-19 vaccines. Specifically, FDA has required each manufacturer to update the warning about the risks

of myocarditis and pericarditis to include information about (1) the estimated unadjusted incidence of myocarditis and/or pericarditis following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines and (2) the results of a study that collected information on cardiac magnetic resonance imaging (cardiac MRI) in people who developed myocarditis after receiving an mRNA COVID-19 vaccine. FDA also required each manufacturer to describe the new safety information in the Adverse Reactions section of the Prescribing Information and in the Information for Recipients and Caregivers.

The Fact Sheets for Healthcare Providers and for Recipients and Caregivers for Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19, which are authorized for emergency use in individuals 6 months through 11 years of age, have also been updated to include the new safety information in alignment with the Comirnaty and Spikevax Prescribing Information and Information for Recipients and Caregivers.

Updated Warning for Myocarditis and Pericarditis
The warning on myocarditis and pericarditis in the Prescribing Information for Comirnaty and Spikevax has been updated to convey that the observed risk of myocarditis and pericarditis following vaccination with mRNA COVID-19 vaccines has been highest in males 12 through 24 years of age and to include the following new language:

- Based on analyses of commercial health insurance claims data from inpatient and outpatient settings, the estimated unadjusted incidence of myocarditis and/or pericarditis during the period 1 through 7 days following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines was approximately 8 cases per million doses in individuals 6 months through 64 years of age and approximately 27 cases per million doses in males 12 through 24 years of age.

- Follow-up information on cardiovascular outcomes in hospitalized patients who had been diagnosed with COVID-19 vaccine-associated myocarditis is available from a longitudinal retrospective observational study. Most of these patients had received a two-dose primary series of an mRNA COVID-19 vaccine prior to their diagnosis. In this study, at a median follow-up of approximately 5 months post-vaccination, persistence of abnormal cardiac magnetic resonance imaging (CMR) findings that are a marker for myocardial injury was common. The clinical and prognostic significance of these CMR findings is not known.

Information about myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) following vaccination with these mRNA COVID-19 vaccines has been included in the labeling since 2021. FDA closely monitors the safety of all vaccines, including the COVID-19 vaccines, during postmarket use.

About the Study on Cardiovascular Outcomes in mRNA COVID-19 Vaccine Recipients Diagnosed With Myocarditis
In a post-approval U.S. study funded and co-authored by FDA and published in September 2024, follow-up information was collected on approximately 300 people who developed myocarditis after receiving the original formula of an mRNA COVID-19 vaccine. Some people in the study reported having heart symptoms approximately 3 months after developing myocarditis. Some people in the study had cardiac MRIs (scans that show detailed images of the heart muscle) initially after developing myocarditis and again approximately 5 months later. The initial and follow-up cardiac MRIs commonly showed signs of injury to the heart muscle, with improvement over time in some but not all people. It is not known if these cardiac MRI findings might predict long-term heart effects of myocarditis.

Safety Monitoring Continues
Continuous monitoring and assessment of the safety of all vaccines, including the mRNA COVID-19 vaccines, is an FDA priority and FDA remain committed to informing the public when FDA learn new information about these vaccines.

In addition, as part of the approvals of Comirnaty and Spikevax, each manufacturer is required by FDA to conduct a study to assess if there are long-term heart effects in people who have had myocarditis after receiving an mRNA COVID-19 vaccine. These studies are underway.

In Hong Kong, there are 4 Comirnaty vaccine products which are registered by Fosun Industrial Co., Limited, namely:

- Comirnaty Dispersion For Injection COVID-19 mRNA Vaccine (Nucleoside

Modified) 30 Micrograms/Dose (HK-67665);
- Comirnaty Original/Omicron BA.4-5 Dispersion For Injection COVID-19 mRNA Vaccine (Nucleoside Modified) (15/15 Micrograms)/Dose (HK-67666);
- Comirnaty Omicron XBB.1.5 Dispersion For Injection COVID-19 mRNA Vaccine (Nucleoside Modified) 30 Micrograms/Dose (HK-68019); and
- Comirnaty JN.1 Dispersion For Injection COVID-19 mRNA Vaccine 30 Micrograms/ Dose (HK-68417).

There are 5 Spikevax vaccine products which are registered by Moderna Hong Kong Limited, namely:
- Spikevax Bivalent Original/Omicron BA.4-5 Dispersion For Injection COVID-19 mRNA Vaccine (Nucleoside Modified) (50 Micrograms/50 Micrograms)/ml (HK-67830);
- Spikevax Bivalent Original/Omicron BA.4-5 Dispersion For Injection In Pre-filled Syringe COVID-19 mRNA Vaccine (Nucleoside Modified) 25 Micrograms/25 Micrograms (HK-67831);
- Spikevax XBB.1.5 Dispersion For Injection In Pre-filled Syringe COVID-19 mRNA Vaccine 50 Micrograms/Dose 0.5ml (HK-68081);
- Spikevax 2023-2024 Formula (XBB.1.5) Suspension For Injection COVID-19 mRNA Vaccine 250 Micrograms/2.5ml (HK-68127); and
- Spikevax JN.1 Dispersion For Injection In Pre -filled Syringe COVID-19 mRNA Vaccine 50 Micrograms/Dose 0.5ml (HK-68388).

All products are prescription-only medicines. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 140, with the latest update reported in the Drug News Issue No. 146. The DH issued letters to inform local healthcare professionals to draw their attention on 28 June 2021. The current product inserts of the locally registered Comirnaty and Spikevax products already include warnings on the risk of myocarditis and pericarditis following vaccination.

In light of the above FDA's announcement with updated warning regarding myocarditis and pericarditis, the DH issued letters to inform local healthcare professionals to draw their attention on 26 June 2025, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board of Hong Kong.

The United States: FDA eliminates Risk Evaluation and Mitigation Strategies (REMS) for Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies

On 26 June 2025, the United States Food and Drug Administration (FDA) announced that the Risk Evaluation and Mitigation Strategies (REMS) for currently approved BCMA- and CD19-directed autologous chimeric antigen receptor (CAR) T cell immunotherapies have been eliminated because the FDA has determined that a REMS is no longer necessary to ensure that the benefits of these CAR T cell immunotherapies outweigh their risks and to minimize the burden on the healthcare delivery system of complying with the REMS.

Background
A REMS is a safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. Because of the risks of cytokine release syndrome (CRS) and neurological toxicities, since their initial approvals until June 2025, the following currently approved (listed alphabetically by trade name) BCMA- or CD19-directed autologous CAR T cell immunotherapies were available through a restricted program under a REMS:
- Abecma (idecabtagene vicleucel)
- Breyanzi (lisocabtagene maraleucel)
- Carvykti (ciltacabtagene autoleucel)
- Kymriah (tisagenlecleucel)
- Tecartus (brexucabtagene autoleucel)
- Yescarta (axicabtagene ciloleucel)

Elimination of the REMS and Updates to Product Labeling
In accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), FDA determined that the approved REMS for these products must be eliminated because a REMS is no longer necessary to ensure that the benefits of the above CAR T cell immunotherapies outweigh their risks, and to minimize the burden on the healthcare delivery system of complying with the REMS. Thus, the REMS for the above products have been eliminated to remove the requirement that hospitals and their associated clinics that dispense the above products are specially certified and have on-site, immediate access to tocilizumab. In addition, product labeling was updated to align with REMS elimination and streamline patient monitoring

following product administration. Specifically, labeling update included revision to language to monitor patients for at least two weeks including daily monitoring for at least one week; to instruct patients to remain within proximity of a healthcare facility for at least two weeks; and to advise patients to avoid driving for two weeks following product administration [Sections 2 (Dosage and Administration), 5 (Warnings and Precautions), 17 (Patient Counseling Information) of the US Prescribing Information and Medication Guide were updated]. FDA expects that the REMS elimination, and these labeling updates, will help improve access to these products, particularly for patients who live in rural areas, while ensuring safe and effective administration to patients who need them.

Given the established management guidelines and extensive experience of the medical hematology/ oncology community in diagnosing and managing the risks of CRS and neurologic toxicities across products in the class of BCMA- and CD19-directed autologous CAR T cell immunotherapies, FDA has determined that the safe and effective use of CAR T cell immunotherapies for the indicated population can be assured without a REMS. Adverse event reporting for CRS and neurological toxicity have remained stable.

The information regarding the risks for these CAR T cell immunotherapies can be conveyed adequately via the current product labeling, which includes a boxed warning for the risks of CRS and neurological toxicities, and the Medication Guides which are a part of the approved labeling.

Safety Monitoring
Continuous monitoring and assessment of the safety of all biological products, including the CAR T cell immunotherapies, is an FDA priority and we remain committed to informing the public when we learn new information about these products.

All CAR T cell immunotherapies will continue to be subject to routine safety monitoring through adverse event reporting requirements in accordance with 21 CFR 600.80.

The elimination of the REMS for these products does not change FDA requirements for manufacturers to conduct post marketing observational safety studies to assess the risk of secondary malignancies and long-term safety with follow up of patients for 15 years after product administration.

In Hong Kong, Kymriah Dispersion for Infusion (HK-66588) is a pharmaceutical product containing tisagenlecleucel registered by Novartis Pharmaceuticals (HK) Limited. It is a prescription-only medicine. The other products mentioned in the above FDA's announcement are not registered pharmaceutical products in Hong Kong. As of the end of June 2025, with regard to tisagenlecleucel, the Department of Health (DH) had received 18 cases of adverse drug reaction, of which 10 cases were reported as cytokine release syndrome, and none of the cases were reported as neurological toxicities.

The current product insert of the locally registered Kymriah product includes safety information that patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome, neurological events and other toxicities. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Also, patients should be instructed to remain within proximity (within 2 hours of travel) of a qualified clinical facility for at least 4 weeks following infusion.

In light of the above FDA's announcement, the DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

Canada: Summary Safety Review: Gadolinium-based Contrast Agents: Assessing the potential risk of serious adverse reactions, including seizures, encephalopathy, coma and death, with intrathecal use

On 27 June 2025, Health Canada announced a Summary Safety Review on Gadolinium-based contrast agents, details as follows:

Product
Gadolinium-based contrast agents (Dotarem [gadoterate meglumine], Gadovist 1.0 [gadobutrol], Magnevist [gadopentetate dimeglumine], MultiHance [gadobenate dimeglumine], Omniscan [gadodiamide], Primovist [gadoxetate disodium] and ProHance [gadoteridol]) (GBCAs)

Potential Safety Issue
Serious adverse reactions, including seizures, encephalopathy (brain dysfunction), coma and

death, with intrathecal (injection into the spinal canal) use

Key Messages

- Health Canada's review found a possible link between the intrathecal use of GBCAs and serious adverse reactions, including seizures, encephalopathy, coma and death.
- Health Canada is working with manufacturers to update the product safety information in the Canadian product monograph (CPM) for all GBCAs to include the risk of serious adverse reactions, including seizures, encephalopathy, coma and death, with off label intrathecal use.

Overview

Health Canada reviewed the potential risk of serious adverse reactions, including seizures, encephalopathy, coma and death with the intrathecal use of GBCAs. The safety review was triggered by a labelling update in the United States for all GBCAs.

Gadolinium-based contrast agents are not authorized in Canada for intrathecal use. However, Health Canada is aware that they have been used off-label for this route of administration.

Use in Canada

- Gadolinium-based contrast agents are authorized for use in magnetic resonance imaging (MRI) to make it easier to view certain body tissues and to help with the diagnosis of various conditions. They are authorized to be given into a vein (intravenously).
- Gadolinium-based contrast agents have been marketed in Canada for over 30 years. There are 7 GBCAs currently marketed under the following brand names: Dotarem, Gadovist 1.0, Magnevist, MultiHance, Omniscan, Primovist and ProHance. A generic version of Gadovist 1.0 is also available.
- From 2019 to 2024, approximately 2.5 million patients in Canada were given GBCAs. However, information on intrathecal usage is not available.

Safety Review Findings

- Health Canada reviewed the available information from the Canada Vigilance database, the scientific literature, and clinical experts.
- Health Canada reviewed 22 cases (1 Canadian and 21 international) of serious adverse reactions, including seizures, encephalopathy, coma and death, in patients who were administered GBCAs intrathecally. Of the 22 cases, 18 (1 Canadian and 17 international) were found to be possibly linked, including 11 from the published literature. The remaining 4 cases could not be assessed due to missing clinical information.
- The dose given was reported in 15 of the 18 cases that were possibly linked to the intrathecal use of GCBAs, and ranged from 1.5 mmol to 12 mmol (median dose 3 mmol).
- All 18 cases that were possibly linked to the intrathecal use of GCBAs involved adult patients. In 17 (1 Canadian) of those cases, the patients recovered or were recovering. A death occurred in the remaining case.
- Health Canada also reviewed the findings from 28 published studies. There were no reports of seizures, encephalopathy, coma or death in patients administered GBCAs intrathecally.

Conclusions and Actions

- Health Canada's review of the available information found a possible link between the intrathecal use of GBCAs and serious adverse reactions, including seizures, encephalopathy, coma and death.
- Health Canada is working with manufacturers to update the CPM for all GBCAs to include the risk of serious adverse reactions, including seizures, encephalopathy, coma and death, with off label intrathecal use.
- Health Canada will continue to monitor safety information involving GBCAs, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action should new health risks be identified.

In Hong Kong, there are registered pharmaceutical products which belong to gadolinium-based contrast agents containing meglumine gadoterate (10 products), gadobutrol (2 products), gadobenic acid (as meglumine gadobenate or gadobenate dimeglumine) (1 product), sodium gadoxetate (gadoxetate disodium) (1 product). All products are prescription-only medicines and are indicated for intravenous administration only.

As of the end of June 2025, according to available information, the Department of Health (DH) had not received any case of adverse drug reaction with regard to intrathecal use of the above gadolinium-based contrast agents. In light of the

above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 27 June 2025, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board of Hong Kong.

Canada: Summary Safety Review: Stivarga (regorafenib): Assessing the potential risk of thrombotic microangiopathy

On 27 June 2025, Health Canada announced a Summary Safety Review on Stivarga (regorafenib), details as follows:

Product
Stivarga (regorafenib)

Potential Safety Issue
Thrombotic microangiopathy (TMA), a rare, but serious and life-threatening, condition involving the formation of clots in small blood vessels

Key Messages
- Health Canada's review found a possible link between Stivarga and the risk of TMA.
- Health Canada will work with the manufacturer to update the product safety information in the Canadian product monograph (CPM) for Stivarga to include the risk of TMA. Health Canada will also inform healthcare professionals about this update through a Health Product InfoWatch communication.

Overview
In 2015, Health Canada reviewed the risk of TMA with the use of vascular endothelial growth factor (VEGF) receptor inhibitors, the drug class to which Stivarga belongs. At that time, although the risk of TMA was recognized for certain VEGF receptor inhibitors (Sutent [sunitinib] and Votrient [pazopanib]), there was insufficient evidence to support a labelling update across the entire drug class. Health Canada committed to continued monitoring of VEGF receptor inhibitors to identify and assess potential harms.

In 2022, Health Canada reviewed the risk of TMA with the use of Nexavar (sorafenib), another VEGF receptor inhibitor. The review determined that there may be a link between the use of Nexavar and the risk of TMA, and Health Canada is working with the manufacturer to update the product labelling for Nexavar. No other VEGF receptor inhibitors were assessed as part of the 2022 review.

In 2024, Health Canada reviewed the potential risk of TMA with the use of Stivarga. This was not a review of the entire VEGF receptor inhibitors drug class. The safety review was triggered by a labelling update by the European Medicines Agency for Stivarga, and an international case report published in the medical literature.

Thrombotic microangiopathy is a rare, but serious and life-threatening, condition involving the formation of clots in the small blood vessels. These clots can cause damage to organs and body systems by blocking proper blood flow. Thrombotic microangiopathy is a medical emergency and requires rapid intervention. A number of factors, including congenital conditions (those present at birth), infection, cancer and drugs, can cause TMA.

Use in Canada
- Stivarga is a prescription drug authorized in Canada for the treatment of:
  - metastatic cancer (cancer that has spread) of the colon and rectum (colorectal) in patients who have already received other treatments,
  - metastatic and/or unresectable (not treatable with surgery) gastric cancer (gastrointestinal stromal tumors) in patients who have had disease progression on or intolerance to other treatments, and
  - patients with liver cancer (hepatocellular carcinoma) as a second line treatment.
- Stivarga has been marketed in Canada since 2013. It is currently available as 40 mg tablets.
- Between September 2018 and August 2024, an estimated 6,000 prescriptions for Stivarga (new and renewals) were dispensed in Canada.

Safety Review Findings
- Health Canada reviewed the available information provided by the manufacturer, as well as from searches of the Canada Vigilance database and the scientific literature.
- At the time of the review, Health Canada had not received any Canadian reports of TMA in patients taking Stivarga.
- Health Canada reviewed 7 international cases of TMA in patients taking Stivarga. Six of the 7 cases, including 1 published in the scientific literature, were found to be possibly linked to the use of Stivarga, while the remaining case was unlikely to be linked. Two deaths were

reported among the 7 cases. It was determined that 1 death was unlikely to be linked to the use of Stivarga, while the second death could not be assessed.
- The evidence from the scientific literature regarding the association between regorafenib and TMA was limited to the trigger case report. While Health Canada reviewed the findings from 2 other publications, they did not provide additional information about the risk of TMA with Stivarga.

Conclusions and Actions
- Health Canada's review of the available information found a possible link between Stivarga and the risk of TMA.
- Health Canada will work with the manufacturer to update the CPM for Stivarga to include the risk of TMA.
- Health Canada will also inform healthcare professionals about this update through a Health Product InfoWatch communication.
- Health Canada will continue to monitor safety information involving Stivarga, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action should new health risks be identified.

In Hong Kong, Stivarga Tab 40mg (HK-63304) is a pharmaceutical product containing regorafenib registered by Bayer Healthcare Limited. It is a prescription-only medicine. As of the end of June 2025, with regard to regorafenib, the Department of Health (DH) had received 36 cases of adverse drug reaction, but these cases were not related to thrombotic microangiopathy.

The current product insert of the locally registered Stivarga product already includes safety information about thrombotic microangiopathy. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

The United States: FDA requires expanded labeling about weight loss risk in patients younger than 6 years taking extended-release stimulants for ADHD

On 30 June 2025, the United States Food and Drug Administration (FDA) announced that action will harmonize labeling across extended-release stimulant drug class.

What safety concern is FDA announcing?
The FDA is revising the labeling of all extended-release stimulants indicated to treat attention-deficit/hyperactivity disorder (ADHD) - including certain formulations of amphetamine and methylphenidate - to warn about the risk of weight loss and other adverse reactions (side effects) in patients younger than 6 years taking these medications.

Although extended-release stimulants are not approved for children younger than 6 years, healthcare professionals can prescribe them "off label" to treat ADHD.

FDA has found that patients younger than 6 years taking extended-release stimulants have a greater risk of weight loss and other side effects than older children taking the same medication at the same dosage. The Agency assessed data from clinical trials of extended-release formulations of amphetamine and methylphenidate for ADHD treatment. This analysis found that patients younger than 6 years have higher plasma exposures (i.e., higher levels of the drug in their bodies) and higher rates of side effects than older children. In particular, clinically significant weight loss (at least 10% decrease in the Centers for Disease Control and Prevention (CDC) weight percentile) was observed in both short- and long-term studies with extended-release stimulants. For these reasons, the benefits of extended-release stimulants may not outweigh the risks of these products in patients younger than 6 years with ADHD.

What is FDA doing?
We are requiring a Limitation of Use section in the prescribing information of all extended-release stimulants that includes a statement about the higher plasma exposures and higher rates of adverse reactions in children younger than 6 years. Manufacturers of extended-release stimulants that do not have a Limitation of Use section in the labeling will be required to add one about this risk. Manufacturers of extended-release stimulants that already have a Limitation of Use section will be required to revise the labeling to ensure consistent messaging across the drug class.

What are extended-release stimulants, and how can they help my child and me?
Extended-release stimulants are prescription drugs primarily used to treat ADHD as first-line (initial) therapy. ADHD is a common childhood disorder that affects the ability to pay attention, follow

directions, and complete tasks. It can continue into adulthood. An estimated 7 million (11.4%) of U.S. children 3 to 17 years of age have been diagnosed with ADHD, with boys (15%) more likely to be diagnosed than girls (8%).

Extended-release stimulants come in a variety of dosage forms, including tablets, capsules, transdermal (skin) patches, and liquid suspensions. Most of them are designed to be taken once a day. Common side effects include loss of appetite, weight loss, and insomnia.

What should parents and guardians do?
If parents or guardians notice weight loss in their child taking an extended-release stimulant for ADHD, they should contact their pediatrician or other healthcare professional to discuss whether the benefits of continued treatment outweigh the risks. Weight loss in young children may contribute to nutritional deficiencies, impaired growth, lower energy levels, and other adverse effects. Parents and guardians can also ask their healthcare professional about alternative treatments for ADHD. Some immediate-release stimulants are approved for children younger than 6 years. Because immediate-release stimulants do not remain in the body for as long, it may be possible to adjust the timing and frequency of dosing to reduce the negative impacts on appetite and sleep. Behavior therapy can also be an effective way to treat ADHD. Parents and guardians should follow their healthcare professional's advice about the most appropriate course of action for their child, which may involve changing or stopping the medication.

What should healthcare professionals do?
Healthcare professionals should be aware that extended-release stimulants are not indicated to treat ADHD in children younger than 6 years because these products have a greater risk of weight loss and other adverse reactions than in older children taking the same dose of the same medication. If a child younger than 6 years is taking an extended-release stimulant and experiencing weight loss or other adverse events, consider stopping the medication and/or switching to an alternative treatment (e.g., immediate-release stimulant). Healthcare professionals should monitor the child's growth and development and provide necessary interventions to mitigate weight loss. Healthcare professionals may prescribe other ADHD medications (e.g., immediate-release stimulants) or provide information about behavioral ADHD therapies.

What is my child's risk?
All medicines may have side effects even when used correctly as prescribed. People respond differently to medicines depending on their health, genetic factors, other medicines they are taking, and many other factors. As a result, FDA cannot determine the likelihood of someone experiencing weight loss or other side effects from taking the medication. Talk to your healthcare professional(s) if you have questions or concerns about this medication's risks.

Facts about extended-release stimulants
- Extended-release stimulants are prescription drugs, including certain formulations of amphetamines and methylphenidate, that are primarily used to treat attention-deficit/ hyperactivity disorder (ADHD) as first-line (initial) therapy.
- These medications increase the activity of the neurotransmitters dopamine and norepinephrine in areas of the brain associated with attention, executive function, and impulse control.
- They come in a variety of dosage forms, including tablets, capsules, transdermal (skin) patches, and liquid suspensions.
- They are designed to be taken once a day.

Additional Information for Parents and Guardians
- FDA is alerting parents and guardians that children younger than 6 years taking extended -release stimulants have a greater risk of weight loss and other side effects than older children taking the same dosage of the same medication.
- Contact your healthcare professional if your child is losing weight and talk to them about whether stopping the extended-release stimulant is appropriate and what other ADHD treatments may be available.

Additional Information for Healthcare Professionals
- Healthcare professionals should be aware that extended-release stimulants are not indicated to treat ADHD in children younger than 6 years.
- FDA has found that patients younger than 6 years experienced higher plasma exposures and higher rates of adverse reactions than older children taking the same dosage of the same medication.

- For children younger than 6 years experiencing weight loss or other adverse reactions while taking extended-release stimulants, healthcare professionals should consider stopping the medication and/or switching to an alternative treatment (e.g., immediate-release stimulant).
- Healthcare professionals may prescribe other medications for ADHD (e.g., immediate-release stimulants) or provide information about behavioral ADHD therapies.
- Healthcare professionals should monitor the child's growth and development and provide necessary interventions to mitigate weight loss.

Data Summary

Through Pediatric Research Equity Act (PREA) postmarketing requirements (PMR), FDA required drug sponsors to evaluate pharmacokinetics (PK), efficacy, and safety of extended-release stimulants in children 4 to 5 years of age. Although the Agency determined that extended-release stimulants are generally safe and effective for older age groups, product labeling for 4 extended-release stimulants include a Limitation of Use statement describing that younger children experienced higher exposures at the same dose relative to older pediatric age groups and higher rates of adverse reactions, including weight loss.

To understand the application of the existing Limitation of Use to all extended-release formulations of amphetamine and methylphenidate, the Agency evaluated differences in PK profiles and exposure-response relationships across pediatric age groups and assessed the short- and long-term effects on weight in children 4 to younger than 6 years of age. Following an assessment of the available clinical trial data in these children, the Agency identified the following:

- Drug exposures were generally higher relative to older children at the same dose
- Higher drug exposures were linked to a greater risk of adverse reactions
- Clinically significant weight loss (at least 10 decrease in the Centers for Disease Control and Prevention (CDC) weight percentile) was observed in both short- and long-term studies with extended-release stimulants
- Findings are consistent for both amphetamine and methylphenidate-containing products

Because the safety profiles for amphetamine and methylphenidate are generally similar and their pharmacodynamic effects are strongly linked to their PK profiles, it is reasonable to expect that that the results of this assessment apply to all formulations of extended-release amphetamine and methylphenidate, and that there is an unfavorable benefit-risk profile for children younger than 6 years taking these medications for ADHD.

In Hong Kong, there are 23 registered pharmaceutical products which are extended-release formulation of methylphenidate. All products are prescription-only medicines and are only indicated for children aged 6 years of age and over. There is no registered pharmaceutical product which is extended-release formulation of amphetamine in Hong Kong.

As of the end of June 2025, according to available information, the Department of Health (DH) had not received any case of adverse drug reaction with regard to use of extended-release formulation of methylphenidate in patients younger than 6 years.

The risk of having higher rates of adverse effects, particularly weight loss, associated with extended-release formulation of methylphenidate in children 4 to less than 6 years of age with ADHD is documented in overseas reputable drug references such as “American Hospital Formulary Service Drug Information”. The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

Drug Incident

Public urged not to buy or use topical products containing undeclared controlled ingredients

On 17 June 2025, the Department of Health (DH) appealed to the public not to buy or use four types of topical products as they were found to contain undeclared controlled drug ingredients. These products include:

Product name	Part 1 poisons found
1. Zangyao xuanduwang	Clobetasol propionate, ketoconazole and miconazole
2. King poison to itch Antibacterial cream	Clobetasol propionate, ketoconazole and miconazole
3. HE SHENG MEI LANG DU WANG	Clobetasol propionate, ketoconazole and miconazole
4. ZHONG HUA ZHEN JUN WANG Antibacterial cream	Clobetasol propionate and miconazole

Acting upon intelligence, the DH has collected samples of the above-mentioned products from a retail stall in Tuen Mun for analysis. Test results from the Government Laboratory revealed that the above products contained undeclared controlled drug ingredients, which are Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap. 138). These products are also suspected to be unregistered pharmaceutical products. The DH, in collaboration with the Police, took enforcement action at the premises today. During the operation, a 51-year-old woman was arrested for suspected illegal sale and possession of Part 1 poisons and unregistered pharmaceutical products. The DH's investigation is still ongoing.

Clobetasol propionate is a steroid substance for treating inflammation. Inappropriate application of steroids could cause skin problems and systemic side effects such as moon face, high blood pressure, high blood sugar, adrenal insufficiency and osteoporosis. Products containing clobetasol propionate are prescription medicines that should be used under a doctor's directions and be supplied in the premises of an Authorized Seller of Poisons (i.e. a pharmacy) under the supervision of a registered pharmacist upon a doctor's prescription.

Ketoconazole and miconazole are used for the treatment of fungal infections with side effects including local irritation and sensitivity reactions. Topical products containing ketoconazole and miconazole should be supplied in a pharmacy under the supervision of a registered pharmacist.

A press release was posted in the Drug Office website on 17 June 2025 to alert the public of the drug incident.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap. 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap. 137) and the maximum penalty is a $50,000 fine and one year's imprisonment for each offence.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.

Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 3904 1224

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920

Fax: 2319 6319

E-mail: adr@dh.gov.hk

Link: http://www.drugoffice.gov.hk/adr.html

Post: Clinical Trials and Pharmacovigilance Unit,
Drug Office, Department of Health,
Suite 2002-05, 20/F, AIA Kowloon Tower, Landmark East,
100 How Ming Street,
Kwun Tong, Kowloon

The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.