Drug News
藥 物 情 報

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This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in June 2024 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

European Union: CAR T-cell medicines: PRAC identifies risk of secondary malignancies of T-cell origin

On 14 June 2024, the European Medicines Agency (EMA) announced that its Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that secondary malignancies of T-cell origin (a new cancer, different from the previous one, that begins in a type of white blood cells of the immune system called T-cells) may occur after treatment with chimeric antigen receptor (CAR) T-cell medicines.

The committee evaluated data on 38 cases of secondary malignancy of T-cell origin, including T-cell lymphoma and leukaemia, reported among approximately 42,500 patients who have been treated with CAR T-cell medicines. Tissue samples were tested in half of the cases, revealing the presence of the CAR construct in 7 cases. This suggests that the CAR T-cell medicine was involved in disease development. The secondary malignancies of T-cell origin have been reported within weeks and up to several years following administration of CAR T-cell medicines. Patients treated with these medicines should be monitored life-long for new malignancies.

CAR T-cell medicines belong to a type of personalised cancer immunotherapies where one type of a patient's white blood cells (T-cells) are reprogrammed and reinjected to attack the cancer.

Six CAR T-cell products are approved in the European Union (EU): Abecma, Breyanzi, Carvykti, Kymriah, Tecartus and Yescarta. These medicines are used to treat blood cancers such as B-cell leukemia, B-cell lymphoma, follicular lymphoma, multiple myeloma and mantle cell lymphoma in patients whose cancer has come back (relapsed) or has stopped responding to previous treatment (refractory).

Since approval, the product information has advised that patients treated with these products may develop secondary malignancies. The product information and the risk management plans will be updated to include the new information concerning secondary malignancy of T-cell origin.

Healthcare professionals will be informed of the PRAC's review conclusion on secondary malignancies of T-cell origin, including chimeric antigen receptor (CAR)-positive malignancies. Healthcare professionals will also be reminded about the need for life-long monitoring of patients for cases of secondary malignancies.

In Hong Kong, Kymriah (tisagenlecleucel) Dispersion for Infusion (HK-66588) is a pharmaceutical product registered by Novartis Pharmaceuticals (HK) Limited. It is a prescription-only medicine. As of the end of June 2024, with regard to tisagenlecleucel, the Department of Health (DH) had received 18 cases of adverse drug reaction, of which 8 cases were reported as malignancies. The other products mentioned in the above EMA's announcement are not registered pharmaceutical products in Hong Kong.

The current product insert of the locally registered Kymriah product already included safety information about secondary malignancies. Related news was previously issued by the United States Food and Drug Administration (US FDA) and EMA, and was reported in Drug News Issue No. 169, 171 and 174. The DH issued letters to inform local healthcare professionals to draw their attention on 24 January 2024.

In light of the above EMA's announcement about

secondary malignancies of T-cell origin, the DH issued letters to inform local healthcare professionals to draw their attention on 17 June 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Warfarin: be alert to the risk of drug interactions with tramadol

On 20 June 2024, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that warfarin and tramadol together can cause harmful drug interactions, which can raise the International Normalised Ratio (INR), and result in severe bruising and bleeding, which in some patients could be fatal.

The MHRA has received a Coroner's report following the death of a patient who died from a bleed on the brain, following concurrent treatment with warfarin and tramadol. Taking warfarin and tramadol together may increase a patient's INR and increase the risk of bleeding. The Coroner raised concerns that the interaction between warfarin and tramadol was not well known and emphasised the need to highlight this interaction to healthcare professionals.

Warfarin is a coumarin-derived vitamin K antagonist used for prevention and treatment of blood clots. It is used to prevent embolisation in rheumatic heart disease and, atrial fibrillation and after insertion of prosthetic heart valves. Warfarin is also used in the prevention and treatment of venous thrombosis and pulmonary embolism and treatment of transient ischaemic attacks.

Warfarin has a low therapeutic index, which means care is required when taking co-prescribed medicines due to the possibility of interactions that could lead to an increased risk of bleeding.

The product information for warfarin advises that healthcare professionals should refer to the product information of any new concomitant medicines for specific guidance on use with warfarin and whether a dose adjustment or therapeutic monitoring is required. The product information will be updated to include the interaction in due course.

Tramadol is a non-selective opioid analgesic, which acts as an agonist at the mu, delta and kappa opioid receptors. Section 4.5 of the tramadol Summary of Product Characteristics states that caution should be exercised during concomitant treatment with coumarin derivatives such as warfarin due to reports of increased INR with major bleeding and bruising in some patients. While the risk of major bleeding with warfarin treatment is rare, the risk may be increased with concurrent use of tramadol.

Advice for healthcare professionals:

- Warfarin is a coumarin-derived vitamin K antagonist which has a low therapeutic index, so continue to exercise caution when co-prescribing warfarin with other drugs, to minimise the risk of drug interactions.
- Ask patients about all the medicines that they are currently taking.
- Be aware of the risk of increased INR when warfarin and tramadol are used together, with a risk of major bruising and bleeding which could be life-threatening.
- Consult the product information of any new concomitant therapy for specific guidance on use with warfarin and consider whether warfarin dose adjustment is required.
- Consider whether additional monitoring of INR is required when starting tramadol or another concomitant medicine.
- Ensure patients are aware of the need to seek medical treatment should they notice the signs of a major bleeding event.
- Caution should also be taken if tramadol is co-prescribed with other coumarin-derived anticoagulants such as acenocoumarol.

In Hong Kong, there are 4 registered pharmaceutical products containing warfarin and 42 products containing tramadol. All products are prescription-only medicines. As of the end of June 2024, with regard to warfarin, the Department of Health (DH) had received 15 cases of adverse drug reaction, of which 2 cases were reported as drug interaction. With regard to tramadol, the DH had received 9 cases of adverse drug reaction, but these cases were not related to drug interaction. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 21 June 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme

On 20 June 2024, the Medicines and Healthcare

products Regulatory Agency (MHRA) announced that Topiramate is now contraindicated in pregnancy and in women of childbearing potential unless the conditions of a Pregnancy Prevention Programme are fulfilled. This follows a review by the MHRA which concluded that the use of topiramate during pregnancy is associated with significant harm to the unborn child. Harms included a higher risk of congenital malformation, low birth weight and a potential increased risk of intellectual disability, autistic spectrum disorder and attention deficit hyperactivity disorder in children of mothers taking topiramate during pregnancy.

Topiramate is indicated for the prophylaxis of migraine and for the treatment of epilepsy. It is available as tablets, a liquid oral solution and as capsules that can be swallowed whole or sprinkled on soft food. The brand name of topiramate is Topamax, and so this may also appear on the box. Topiramate has been contraindicated in pregnancy for the prophylaxis of migraine since 2010.

Following a comprehensive review of the safety of antiseizure medications in pregnancy, including topiramate, new safety advice was published in January 2021. Since then, new study data has become available reporting a potential increased risk of autism spectrum disorder and effects on learning development in children exposed to topiramate during pregnancy. These new data, and data suggesting increasing use of topiramate in women of childbearing age, triggered a new safety review. This review examined the available data on the risk of congenital malformations, effects on growth and development of the baby, and the risk of neurodevelopmental disorders when topiramate is used during pregnancy.

The review concluded that the use of topiramate during pregnancy is associated with significant harm to the unborn child (both from the confirmed risks of congenital malformations and low birth weight and the potential risk of neurodevelopmental disorders). The accumulating data suggest that:

- Topiramate is amongst the antiseizure medications associated with a higher risk of congenital malformations (approximately 4 to 9 per 100 babies compared to around 1 to 3 babies in every 100 in the general population)
- The risk of congenital malformations with topiramate appears to be dose-dependent, however, a threshold dose below which no risk exists cannot be established
- Topiramate is associated with a high prevalence of babies being born small for gestational age and weighing less at birth (approximately 18 per 100 babies affected); this is higher than the risk in babies born to women with epilepsy not taking antiseizure medication (approximately 5 in 100 babies affected) and may be higher than the risk with some other antiseizure medications
- Topiramate may be associated with an approximately 2 to 3 times increased risk of intellectual disability, autistic spectrum disorders and attention deficit hyperactivity disorder compared with children born to mothers with epilepsy not taking antiseizure medication.

Due to the accumulating data on these harms, further restrictions are being introduced with regards to the use of topiramate in women of childbearing potential and in pregnancy. The use of topiramate is now contraindicated:

- in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (for all indications)
- in pregnancy for prophylaxis of migraine
- in pregnancy for epilepsy unless there is no other suitable treatment.

General advice for healthcare professionals:

- Topiramate should not be used in pregnancy for prophylaxis of migraine, and in pregnancy for epilepsy unless there is no other suitable treatment.
- Topiramate should not be used in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled. This aims to ensure that all women of childbearing potential are using highly effective contraception, have a pregnancy test to exclude pregnancy before starting topiramate and are aware of the risks from use of topiramate.

In Hong Kong, there are 26 registered pharmaceutical products containing topiramate. All products are prescription-only medicines. As of the end of June 2024, with regard to topiramate, the Department of Health (DH) had received 5 cases of adverse drug reaction, but these cases were not related to birth defects.

Currently, the package insert and/or sales pack label of locally registered topiramate-containing

products should include safety information on fetal harm and the increased risk of cleft lip and/or cleft palate (oral clefts) in infants exposed to topiramate in utero. Related news on the risk of birth defects associated with the use of topiramate during pregnancy was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 153, with the latest update reported in Drug News Issue No. 167. The DH issued letters to inform local healthcare professionals to draw their attention on 4 September 2023. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: Summary Safety Review: Nexavar (sorafenib): Assessing the potential risk of tumour lysis syndrome

On 27 June 2024, Health Canada announced that it reviewed the potential risk of tumour lysis syndrome (TLS) with the use of Nexavar. The safety review was triggered by a labelling update made by the European Medicines Agency and international case reports published in the medical literature.

TLS is a potentially life-threatening condition that can occur during cancer treatment. When cancer cells are killed by the cancer treatment, they release their contents (salts and proteins) into the blood. When cancer cells break down faster than the kidneys can remove these substances from the blood, it can cause changes to the chemical balance in the blood, which may result in damage to organs, most commonly the kidneys, heart and brain.

Health Canada reviewed information provided by the manufacturer, and from searches of the Canada Vigilance database, international databases and the scientific literature. At the time of the review, Health Canada had not received any Canadian reports of TLS in patients taking Nexavar.

Health Canada reviewed 9 international cases of TLS in patients taking sorafenib, including 8 from the published literature. All 9 cases were found to be possibly linked to the use of sorafenib, although a potential contribution from spontaneous TLS (cancer cell break down in the absence of treatment) could not be ruled out. The reported time to the onset of TLS ranged from 3 to 34 days after starting treatment with sorafenib. Five deaths were reported among the 9 cases assessed. All 5 deaths were found to be possibly linked to TLS from sorafenib treatment. However, other causes of death, such as cancer progression, could not be ruled out.

Health Canada reviewed 1 additional article published in the scientific literature. A link between sorafenib and TLS could not be established due to study limitations.

Health Canada's review found a possible link between the use of Nexavar and the risk of TLS. Health Canada is working with the manufacturer to update the Canadian product monograph for Nexavar to include the risk of TLS. Health Canada will also inform healthcare professionals about this update through a Health Product InfoWatch Communication.

In Hong Kong, there are 5 registered pharmaceutical products containing sorafenib. All products are prescription-only medicines. As of the end of June 2024, with regard to sorafenib, the Department of Health (DH) had received 20 cases of adverse drug reaction, but the cases were not related to TLS. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 28 June 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: Summary Safety Review: Iodinated contrast Medium: Assessing the potential risk of hypothyroidism in children under 3 years of age

On 27 June 2024, Health Canada announced that it reviewed the potential risk of transient (temporary) or permanent hypothyroidism with the use of iodinated contrast medium (ICM) products in children and adults in 2017. The Department concluded that there is a risk of rare cases of hypothyroidism with the use of these products in certain patients, mostly infants (less than 1 year of age). The Canadian product monographs (CPMs) of all reviewed ICM products were updated to include this risk.

Since 2017, new studies evaluating this risk have been published. In 2023, Health Canada reviewed these new studies and the earlier ones published in the medical literature that assessed the potential risk of hypothyroidism in children under 3 years of age who were exposed to ICM products. The safety review was triggered by a labelling update in the U.S. for children 3 years of age or younger.

Safety Update

Hypothyroidism in young children may be harmful for neurological (brain) and cognitive (how children think and understand) development.

Health Canada reviewed information from searches of the Canada Vigilance Database, international databases, and the scientific literature. At the time of the review, Health Canada had not received any Canadian reports of hypothyroidism related to the use of ICM products in children.

Health Canada reviewed 18 articles published in the scientific literature, including 2 studies published since the 2017 review that were conducted in a larger population of children. Overall, the evidence reviewed was limited, but suggested an association between hypothyroidism and ICM exposure in children under 3 years of age. Most cases in these studies reported that hypothyroidism was temporary and did not require treatment.

The rate of hypothyroidism was found to be higher in children under 3 years of age with the following risk factors: very low birth weight, prematurity, and the presence of cardiac and other conditions, such as admission to intensive care units.

Health Canada's review of the available information concluded that there is a potential risk of hypothyroidism with the use of ICM products in children under 3 years of age. Younger age, very low birth weight, prematurity, and the presence of cardiac or other conditions, such as admission to intensive care units, are associated with a higher risk of hypothyroidism after exposure to ICM products. Despite the limited available evidence, the seriousness and life-long effects on the cognitive and neurological development of children under 3 years of age warrant a precautionary approach.

Health Canada will work with the manufacturers to update the CPM of all ICM products to provide additional information about the risk of hypothyroidism in children under 3 years of age and recommend monitoring of young children based on their risk factors. Health Canada will also inform healthcare professionals about this update through a Health Product InfoWatch communication.

In Hong Kong, there are registered pharmaceutical products which are iodine-containing contrast agents containing iodixanol (2 products), iopromide (2 products), ioversol (4 products), iohexol (2 products), iodised oil (1 product), iopamidol (2 products) and mixture of meglumine amidotrizoate and sodium amidotrizoate (1 product). There is no registered pharmaceutical product containing iothalamate meglumine. As of the end of June 2024, the Department of Health (DH) had received adverse drug reaction with regard to iodixanol (3 cases), iopromide (48 cases), iohexol (2 cases), iodised oil (2 cases), iopamidol (6 cases), but these cases were not related to hypothyroidism. The DH had not received any case of adverse drug reaction with regard to ioversol and mixture of meglumine amidotrizoate and sodium amidotrizoate.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 73, with the latest update reported in Drug News Issue No. 162. The DH issued letters to inform local healthcare professionals to draw their attention on 18 November 2015 and 31 March 2022. In April 2016, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the sales pack labels and/or package inserts of iodine-containing contrast agents should include safety warnings on the risk of hypothyroidism. As previously reported, the matter will be further discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Batch recall of Ferrum Hausmann Drops 50mg/ml

On 17 June 2024, the Department of Health (DH) endorsed a licensed drug wholesaler, namely Hong Kong Medical Supplies Ltd (HKMS), to recall eight batches (batch numbers: AAL56301, AAM03804, AAP27103, AAR88304, AAT62402, AAW72104, NAA04302 and NAA14002) of Ferrum Hausmann Drops 50mg/ml (Hong Kong Registration Number: HK-36593) from the market as a precautionary measure due to a potential quality issue.

The DH received notification from HKMS that the overseas manufacturer of the product is initiating a voluntary recall of the above batches due to the presence of small plastic particles above the cap of

the dropper in some samples of the product; the particles may fall out when used. As a precautionary measure, HKMS is voluntarily recalling the affected batches of product from the market. The DH's investigation is continuing.

The above product, containing iron, is an over-the-counter medicine for the treatment of iron deficiency and iron deficiency anaemia. According to HKMS, the concerned batches of product have been imported into Hong Kong for distribution to the Hospital Authority, local private hospitals, private doctors and pharmacies, as well as for re-export to Macao.

As of the end of June 2024, the DH had not received any adverse drug reaction reports related to the affected batches of product. A press release was posted in the Drug Office website on 17 June 2024 to alert the public of the product recall. The DH will closely monitor the recall.

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/reListRPP_index.html.

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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.