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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 May 2018 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

Canada: Several GlaxoSmithKline Inc. vaccines: Potential risk of underdosing

On 1 May 2018, Health Canada announced that there have been reports of leakage from ceramic coated tip (CCT) syringes used for several GlaxoSmithKline Inc. vaccines during vaccine preparation or administration. Although the leakage does not pose a concern for the vaccine sterility, there is a potential risk of underdosing associated with administration of a vaccine from a leaking syringe that may leave patients inadequately protected from disease after vaccination. The products affected include: BOOSTRIX, BOOSTRIX-POLIO, ENGERIX-B (Adult), HAVRIX, HAVRIX Junior, INFANRIX-IPV, INFANRIX-IPV/HIB, INFANRIX-hexa, TWINRIX and TWINRIX Junior.

Beginning in July 2015, GlaxoSmithKline Biologicals SA identified an increase in the reporting rate of leakages in CCT syringes at the connection of the syringe tip and the needle hub during vaccine preparation and administration. The integrity of the leaking syringe and sterility of the contents were not compromised. A review of GlaxoSmithKline Biologicals SA pharmacovigilance data as of 14 December 2017 did not find evidence that the observed leakage has resulted in vaccination failure (lack of efficacy) or any other patient safety concern. In Canada, the syringe leakage rate is 3 per 100,000 syringes distributed, although the precise frequency of leakage is not known and may be higher.

GlaxoSmithKline Inc. has implemented corrective actions with its syringe suppliers and has introduced improved syringes in its filling operations as of January 2018. However, both the improved and current CCT syringes will be on the market during 2019, with the proportion of potentially affected syringes progressively decreasing towards the end of 2019 by when the current syringes are expected to have been used up.

Data relevant to the administration of lower antigen content are available for HAVRIX and ENGERIX-B. These data suggest that the administration of half the required antigen dose of HAVRIX or ENGERIX-B will not affect seroprotection or seropositivity. As the probability of a leakage resulting in patients receiving half the required dose is very low, leakage is not expected to impact seroprotection or seropositivity following vaccination. No dose-range studies are available for TWINRIX, but the immune response to the two antigens in the TWINRIX vaccine was demonstrated to be at least as good as that after vaccination with the monovalent vaccines, HAVRIX and ENGERIX-B, for which data on administration of lower antigen content are available. For the other vaccines potentially impacted by leakages, it is not possible to assess the likely impact of underdosing on seroprotection or seropositivity. However, for vaccines given in a multi-dose schedule (2-3 priming doses plus booster), it is highly unlikely that each dose will be administered with a leaking syringe.

Regarding the potential risk of overdosing in case of revaccination, the reported adverse events after overdosage with vaccines, including INFANRIX-IPV and INFANRIX-IPV/Hib, BOOSTRIX, BOOSTRIX-POLIO and TWINRIX, were similar to those reported with the standard dose administration.

Healthcare professionals are advised:

- not to use the syringe when the leakage occurs during reconstitution of lyophilized vaccines.
- when the leakage occurs during vaccine injection and the individual received less than the standard dose, the decision to revaccinate should take into account both the potential benefits and risks associated with administering a repeated dose.

In Hong Kong, according to GlaxoSmithKline Limited (GSK), the following 17 registered pharmaceutical products, namely Boostrix Vaccine (HK-48297), Boostrix Polio Vaccine (HK-55589), Boostrix Polio Vaccine (DH PACK) (HK-62558), Engerix-B 10 Junior Vaccine Suspension for Injection in Prefilled Syringe 10mcg/0.5ml (HK-65375), Engerix-B 20 Adult Vaccine Suspension for Injection in Prefilled Syringe 20mcg/1ml (HK-65374), Havrix 720 Junior Vaccine (HK-42693), Havrix 1440 Vaccine (HK-40826), Infanrix Hexa Vaccine (HK-48745), Infanrix Hexa Vaccine (HK-62935), Infanrix Hexa Vaccine (HK-64010), Infanrix-IPV Vaccine Prefilled Syringe (HK-49556), Infanrix-IPV+Hib Vaccine (HK-47367), Infanrix IPV-Hib Vaccine (HK-62548), Priorix Powder for Inj Vaccine (Live) (HK-43861), Priorix-Tetra Vaccine (HK-57798), Twinrix Adult Vaccine (HK-43814) and Twinrix Junior Vaccine Inj (HK-44500), are affected by the incident. All products are prescription-only medicines.

As on 5 June 2018, the Department of Health (DH) has received a total of 15 cases of adverse drug reaction (ADR) associated with the affected vaccines registered by GSK including 4 cases related to Boostrix Polio, 2 cases related to Engerix -B Junior, 1 case related to Engerix-B Adult, 4 cases related to Infanrix Hexa, 3 cases related to Infanrix IPV-Hib and 1 case related to Priorix-Tetra, but these cases were not related to leakage and underdosing. DH has not received any case of ADR related to Boostrix, Havrix Junior, Havrix, Infanrix-IPV, Priorix, Twinrix Adult and Twinrix Junior.

In light of the above Health Canada's announcement, DH has contacted GSK to follow up on the local impact of the incident. DH issued a letter to inform local healthcare professionals to draw their attention on the above safety information on 9 May 2018. DH also notes that GSK issues letters with deliveries of the affected vaccines to inform its clients. DH will remain vigilant on safety update of the products issued by other overseas drug regulatory authorities.

Singapore: Update on canagliflozin and risk of lower limb amputation

On 11 May 2018, Health Sciences Authority (HSA) of Singapore announced an update on canagliflozin and risk of lower limb amputation (LLA).

In May 2016, a Dear Healthcare Professional Letter (DHCPL) was issued by the company (Johnson & Johnson Pte Ltd) to inform healthcare professionals about an increased risk of LLA with canagliflozin observed in an ongoing long-term cardiovascular outcome trial (CVOT), called the Canagliflozin Cardiovascular Assessment Study (CANVAS). This article provides an update on the LLA-related safety findings.

The CANVAS program comprised two sister studies, CANVAS and CANVAS-Renal (CANVAS-R), which were similar in study design and subject eligibility criteria. The CANVAS and CANVAS-R studies were initiated in December 2009 and January 2014, respectively, and both studies were completed in February 2017. Patients treated with canagliflozin had a lower risk of cardiovascular (CV) events than those who received placebo. However, an approximately two-fold increased risk of LLA (primarily of the toe and midfoot) was observed in patients treated with canagliflozin compared to placebo. The imbalance in LLA incidence occurred as early as the first 26 weeks of therapy, and in a dose-independent manner. Multiple amputations (some involving both lower limbs) were observed infrequently and in similar proportions in both treatment groups. Regardless of treatment with canagliflozin or placebo, the risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease and neuropathy. Lower limb infections, diabetic foot ulcers, peripheral arterial disease and gangrene were the most common medical events associated with the need for an amputation in both

treatment groups.

As on 11 May 2018, the evidence suggesting an increased risk of LLA with sodium-glucose cotransporter-2 inhibitors (SGLT2) inhibitors other than canagliflozin is limited. The CVOT for empagliflozin, known as the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) study, did not systematically capture the amputation events. A total of 7,020 type 2 diabetes mellitus patients with high CV risk, 99.5% of which had pre-existing CV disease, were enrolled in this study. Post-hoc analysis of LLA-related adverse events identified in this study found no difference in the risk of LLA between empagliflozin and placebo (HR 1.00 [95% CI 0.70, 1.44]). The CVOT of dapagliflozin, known as Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), is ongoing and expected to be completed in July 2018.

As on 11 May 2018, HSA has not received any reports of LLA associated with canagliflozin or other SGLT2 inhibitors in Singapore. Following the issuance of the DHCPL in May 2016, the package inserts (PIs) for Invokana™ containing canagliflozin in Singapore was updated to warn about the risk of LLA, and is currently in the process of being updated to include findings from the integrated analysis of the CANVAS program. Healthcare professionals are advised to take into consideration the above safety information when prescribing canagliflozin, and to monitor canagliflozin-treated patients for complications which may precede LLA, such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene. They should also consider counselling their patients about the importance of routine preventive foot care and maintaining adequate hydration. HSA will continue to closely monitor the Singapore and international developments regarding the risk of LLA with SGLT2 inhibitors and will update healthcare professionals of any new significant findings. Healthcare professionals are encouraged to report any serious adverse reactions, including amputations, related to SGLT2 inhibitors to the Vigilance and Compliance Branch of HSA.

In Hong Kong, there are 2 registered pharmaceutical products containing canagliflozin, namely Invokana Tablets 100mg (HK-63499) and Invokana Tablets 300mg (HK-63500). Both products are registered by Johnson & Johnson (Hong Kong) Ltd., and are prescription-only medicines.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 78 and 88. DH issued a letter to inform local healthcare professionals to draw their attention on the warnings on 18 April 2016. In September 2017, the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee) discussed the matter and decided that the labelling of canagliflozin should include information on the risk of lower limb amputation.

As on 5 June 2018, DH has received 2 cases of ADR related to canagliflozin, but none of these cases were related to lower limb amputation. DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Singapore: Gadolinium-based contrast agents and risk of gadolinium brain deposits

On 11 May 2018, HSA announced that it has recently completed its benefit-risk assessment on the potential risk of gadolinium deposition in the brain following repeated administration of gadolinium-based contrast agents (GBCAs). This assessment was triggered by recent findings from scientific publications suggesting that gadolinium is retained in the brain after use of GBCAs in magnetic resonance imaging (MRI) scans, as well as the European Medicines Agency's (EMA) decision to suspend the marketing authorisations of selected intravenous (IV) linear GBCAs and restrict the use of another IV linear GBCA in July 2017. HSA's review concluded that while there is currently no definite evidence of clinical harm of gadolinium brain deposition following GBCA administration, healthcare professionals are advised to use the lowest effective dose of GBCA whenever possible as a precautionary measure.

Initial brain imaging studies documented hyperintensities in brain MRI scans of patients who had received multiple GBCAs administrations,

leading to the hypothesis that gadolinium is deposited in the brain after repeated GBCA use. This hypothesis was confirmed by post-mortem studies documenting the presence of gadolinium in harvested brain tissues of deceased individuals who had been exposed to repeated GBCAs during their lifetime. In addition, the evidence for gadolinium deposition had been found to be much stronger with the less stable linear GBCAs as compared to the macrocyclic agents, suggesting that the propensity of a GBCA to cause brain deposition could be related to the chemical structure and stability of the GBCA chelate. Based on the current available scientific evidence, the presence of gadolinium brain deposits has not been shown to result in clinical adverse effects and the long-term effects are still being studied.

International regulatory health authorities, namely EMA, the United States (US) Food and Drug Administration (FDA), Health Canada, Australia Therapeutic Goods Administration (TGA) and New Zealand Medsafe had conducted safety reviews on the potential risk of gadolinium brain deposition following administration of GBCAs. While all the reviews of these agencies concluded that there was no clinical harm that could be directly attributed to gadolinium brain deposition, EMA recommended the suspension of the marketing authorisations of three IV linear GBCAs (gadopentetic acid, gadodiamide and gadoversetamide) while restricting the use of the IV formulation of the linear agent gadobenic acid to liver scans only as a precautionary measure. No additional restrictions were instituted for macrocyclic GBCAs but EMA advised that they should be used at the lowest doses that enhanced images sufficiently and only when unenhanced body scans were not suitable. The other agencies did not suspend the use of linear GBCAs but strengthened the PIs of the approved GBCAs (both linear and macrocyclic) in their jurisdictions to include information on this potential risk.

HSA's assessment took into consideration findings from scientific literature, information provided by the drug companies, usage of GBCAs in Singapore, expert opinions of radiologists in Singapore, and actions taken by the international regulatory health authorities. An advisory issued by the College of Radiologists Singapore in 2017 had shared that there was no definitive evidence of Parkinson's disease or other neurological diseases linked to GBCAs. It also stated that GBCAs had a long history of use with clear benefits to patients without major long-term side effects.

HSA has assessed that linear GBCAs still have a place in clinical practice in Singapore, particularly in specialised MRIs such as liver and cardiac imaging. Scientific evidence has shown that gadolinium accumulates in brain tissues following multiple GBCA administrations, with a tendency towards higher gadolinium deposition with the linear agents as compared to macrocyclic agents. However, no adverse clinical consequences have been identified and the long-term clinical significance of gadolinium deposition is presently unknown.

As on 11 May 2018, HSA has not received any reports of adverse events arising from the accumulation of gadolinium in brain tissues. A DHCPL was issued in March 2018 to enhance healthcare professionals' awareness to this safety issue. HSA is working with the companies to strengthen the PIs of GBCAs in Singapore to warn of the potential risk of gadolinium brain deposits.

While the benefit-risk profile of linear GBCAs remains favourable, HSA would like to advise healthcare professionals, in particular radiologists, of the following as a precautionary measure:

- Consider the retention characteristics of each GBCA when choosing GBCAs for patients.
- Use the lowest effective dose of GBCA whenever possible and repeated doses of GBCAs should be administered only after careful benefit-risk assessment.
- Closely monitor patients who have been administered GBCAs and to report any serious adverse events suspected to be associated with GBCA use.

HSA will continue to monitor the international and Singapore developments regarding this safety issue and update healthcare professionals of any new significant findings. Healthcare professionals are encouraged to report any serious adverse events suspected to be related to GBCAs to the Vigilance and Compliance Branch of HSA.

In Hong Kong, there are 8 registered pharmaceutical products which are gadolinium contrast agents, and are prescription-only medicines, including Magnevist Inj (HK-32608) containing meglumine gadopentetate, Omniscan Inj 0.5mmol/ml (HK-43493) containing gadodiamide, Gadovist Inj 1mmol/ml (HK-51750) and Gadovist Inj 1mmol/ml (Pre-filled Syringe) (HK-57330) containing gadobutrol, Primovist Pre-filled Syringe Inj 0.25mmol/ml (HK-54116) containing sodium gadoxetate, Dotarem Inj. 377mg/ml (Vial) (HK-41578) and Dotarem Prefilled Syringes, 377mg/ml (HK-41579) containing meglumine gadoterate, and MultiHance Inj 334mg (HK-57789) containing gadobenic acid (as meglumine gadobenate).

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 69, 87, 91, 93 and 98. DH issued a letter to inform local healthcare professionals to draw their attention on 24 July 2017. As on 5 June 2018, DH has received 7 cases of ADR in connection with gadolinium contrast agents: 2 cases on Omniscan, 3 cases on Dotarem, and 2 cases on Gadovist, but all these ADR cases were not related to gadolinium deposition in brain tissues. The matter has been discussed by the Registration Committee on 12 June 2018 and decided that the sales pack labels and/or package inserts of registered pharmaceutical products containing GBCAs should include recommendations in-line with US FDA.

Singapore: Caution on the use of lysozyme-containing products in patients with known egg allergy

On 11 May 2018, HSA announced that it would like to inform healthcare professionals that lysozyme that is present in lysozyme-containing therapeutic products is derived from egg white, and hence these products have the potential to cause allergic reactions in patients with egg allergies. HSA has recently received an ADR report of severe cough, urticaria and eczema flare in a child with known egg allergy who was given lysozyme. As on 11 May 2018, other ADRs reported with lysozyme-containing products were mainly eye swelling and rashes. HSA will be working with the companies' marketing lysozyme-containing products to update the respective product information labels on this safety information.

Healthcare professionals are advised to check with their patient for any history of egg allergy before prescribing or dispensing lysozyme-containing products to their patients. They are also encouraged to report any suspected serious ADRs related to these products to the Vigilance and Compliance Branch of HSA.

In Hong Kong, there are 253 registered pharmaceutical products containing lysozyme. As on 5 June 2018, DH has not received any case of ADR related to lysozyme. In light of the above HSA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 18 May 2018. DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

EU: PRAC recommends new measures to minimise risk of rare but serious liver injury with Esmya for fibroids - Regular liver function testing required during treatment

On 18 May 2018, EMA of the European Union (EU) announced that EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of Esmya (ulipristal acetate), following reports of serious liver injury. After considering all the evidence, PRAC concluded that the medicine must not be used in women with liver problems and that certain other patients may start new treatment courses provided they have regular liver tests.

Esmya is used to treat moderate to severe symptoms of uterine fibroids (benign tumours of the womb). The medicine has been shown to be effective at reducing bleeding and anaemia, as well as the size of the fibroids.

PRAC has concluded that Esmya may have contributed to the development of some cases of serious liver injury. PRAC has therefore made the following recommendations to minimise this risk:

- Esmya must not be used in women with known liver problems.
- A liver function test should be performed before starting each treatment course and

treatment must not be started if liver enzyme levels are more than 2 times the upper limit of normal.
- Liver function tests should be performed once a month during the first two treatment courses and two to four weeks after stopping treatment. If the test is abnormal (liver enzyme levels more than 3 times the upper limit of normal), the doctor should stop treatment and closely monitor the patient.
- Esmya should be used for more than one treatment course only in women who are not eligible for surgery. Women who are about to have surgery should continue to use only one course.
- A card will be included in the box of the medicine to inform patients about the need for liver monitoring, and to contact their doctor should they develop symptoms of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting).
- Studies should be performed to determine the effects of Esmya on the liver and whether these measures are effectively minimising the risks.

In February 2018, while the review was ongoing, PRAC had issued temporary recommendations that no new patients should be started on Esmya. Having finalised its review, PRAC has now concluded that new patients can start treatment in line with the above recommendations to minimise the risk of liver injury.

In Hong Kong, Esmya Tablets 5mg (HK-62553) containing ulipristal acetate is a pharmaceutical product registered by Orient Europharma Co. Ltd, and is a prescription-only medicine. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 98 and 100. DH issued a letter to inform local healthcare professionals to draw their attention on 12 February 2018. As on 5 June 2018, DH has not received any case of ADR related to ulipristal acetate for uterine fibroids. As the review of the drug by Health Canada is ongoing, and the EMA's final recommendation is awaiting, DH will remain vigilant on the conclusion of these review and recommendation, and safety update of the drug issued by other overseas drug regulatory authorities.

EU: PRAC confirms its recommendation to suspend hydroxyethyl-starch (HES) solutions for infusion in the EU

On 18 May 2018, EMA announced that following a request from the European Commission (EC) to look into certain aspects related to the suspension of the marketing authorisations for hydroxyethyl starch (HES) solutions for infusion, EMA's PRAC has confirmed its recommendation to suspend these products across EU.

In January 2018, PRAC recommended suspending the marketing authorisations for HES solutions for infusion because they continued to be used in critically ill patients and patients with sepsis despite restrictions introduced in 2013 to reduce the risk of kidney injury and death in such patients.

This recommendation was endorsed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and sent to EC. In April 2018, EC requested PRAC to consider whether suspending the marketing authorisations could result in an unmet medical need. It also requested PRAC to consider the feasibility and likely effectiveness of additional risk minimisation measures.

After having assessed the relevant data on these specific aspects, PRAC confirmed its previous recommendation that HES solutions for infusion should be suspended. The PRAC recommendation will be sent to CMDh for consideration at its meeting on 28-30 May 2018.

In Hong Kong, there are 6 registered pharmaceutical products containing hydroxyethyl starch, namely Voluven Infusion 6% (HK-50474) and Volulyte 6% Solution for Infusion (HK-58087) registered by Fresenius Kabi Hong Kong Limited, Tetraspan 6% Solution for Infusion (HK-56978) and Tetraspan 10% Solution for Infusion (HK-56979) registered by B. Braun Medical (HK) Ltd, and Hestar-200 Inj. 10% (HK-57095) and Hestar-200 Inj. 6% (HK-57096) registered by Unico & Co. All products are prescription-only medicines.

Related news on increased risks of death and kidney injury in critically ill patients was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 44, 48, 50, 99 and 102. DH issued letters to inform local healthcare professionals to draw their attention on the above risks on 17 June 2013 and 15 January 2018.

The Registration Committee first discussed the matter in the meeting on 5 December 2013, and decided that DH will remain vigilant on the final version of the warnings by EU health authority and the final legally binding decision by EC for further consideration. On 23 October 2013, CMDh endorsed the recommendation of PRAC and concluded that HES solutions must no longer be used to treat patients with sepsis or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality. Subsequently, EC endorsed it on 19 December 2013 for the adoption of a final legally binding decision valid throughout EU.

On 12 April 2018, the Registration Committee further discussed the suspension of the marketing authorisations for HES solutions for infusion across EU, and having considered the local situation, decided to keep vigilant on any update on the issue from other regulatory authorities.

As on 5 June 2018, DH has not received any case of ADR related to hydroxyethyl starch. In light of the above EMA's announcement, DH will remain vigilant on the development of this issue and any updates of recommendation of hydroxyethyl starch issued by other overseas regulatory authorities.

EU: New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir – While EMA review is ongoing, dolutegravir should not be used in women seeking to become pregnant

On 18 May 2018, EMA announced that it is evaluating preliminary results from a study which found 4 cases of birth defects such as spina bifida (malformed spinal cord) in babies born to mothers who became pregnant while taking dolutegravir. While EMA is assessing the new evidence it has issued the following precautionary advice:

- Dolutegravir human immunodeficiency virus (HIV) medicines should not be prescribed to women seeking to become pregnant.
- Women who can become pregnant should use effective contraception while taking dolutegravir medicines.

Dolutegravir is an integrase inhibitor. This means that it blocks an enzyme called integrase that is needed by the HIV virus to make new copies of itself in the body. When it is given with other medicines, it helps to prevent the spread of HIV and keep the amount of the virus in the blood at a low level. Dolutegravir does not cure HIV infection or acquired immunodeficiency syndrome (AIDS), but it may hold off damage to the immune system and the development of infections and diseases associated with AIDS.

The study, which looked at babies born to 11,558 HIV-infected women in Botswana, showed that 0.9% of babies (4 of 426) whose mothers became pregnant while taking dolutegravir had a neural tube defect, compared with 0.1% of babies (14 of 11,173) whose mothers took other HIV medicines. Final results are expected in about a year.

Women who have been prescribed dolutegravir should not stop taking their medicine without first consulting their doctor.

EMA will update the recommendations as necessary when it concludes its assessment.

Information for patients

- Preliminary data show that taking dolutegravir for HIV before pregnancy may increase the risk of birth defects such as spina bifida (malformed spinal cord).
- If patients are taking dolutegravir and they can become pregnant they should use an effective contraception.
- If patients are taking dolutegravir and wish to become pregnant, they should talk to the doctor about whether dolutegravir remains the most appropriate treatment.
- If patients are pregnant and using dolutegravir, they should consult the doctor. They should not discontinue dolutegravir without consulting the doctor, as this may

harm them and their unborn children.
- Tell the doctor for review of treatment if patients become pregnant, think they might be pregnant or are planning to become pregnant.
- If patients have any questions about the treatment or contraception, speak to the doctor or pharmacist.

Information for healthcare professionals

- Preliminary results from an observational study revealed an increased risk of neural tube defects in infants born to women who took dolutegravir at the time of conception. No cases were reported in infants born to women who started dolutegravir later during pregnancy.
- Reproductive toxicology studies have not shown any relevant findings. Likewise, other data on the use of dolutegravir in pregnancy, including data from the Antiretroviral Pregnancy Registry, clinical trials and post-marketing use have not indicated a risk of neural tube defects.
- As a precaution, healthcare professionals in EU are advised of the following:
  - Do not prescribe dolutegravir for women of child bearing potential (WOCBP) who are trying to become pregnant.
  - Exclude pregnancy in WOCBP before starting dolutegravir.
  - Advise WOCBP who are taking dolutegravir to use effective contraception throughout treatment.
  - If pregnancy is confirmed in the first trimester while a woman is taking dolutegravir, switch to an alternative treatment unless there is no suitable alternative.

In Hong Kong, there are 2 registered pharmaceutical products containing dolutegravir, namely Tivicay Tablets 50mg (HK-63516) and Triumeq Tablets (HK-64012). Both products are registered by GSK, and are prescription-only medicines. As on 5 June 2018, DH has received 3 cases of ADR related to dolutegravir, but these cases were not related to birth defects.

Related news was issued by US FDA on the same date. In view of EMA and US FDA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 21 May 2018. While EMA's review is ongoing, DH will keep vigilant on any further update from EMA, US FDA and other health authorities.

US: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq)

On 18 May 2018, US FDA alerted the public that serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir used to treat HIV. Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects.

Neural tube defects are birth defects that can occur early in pregnancy when the spinal cord, brain, and related structures do not form properly. As on 18 May 2018, in this observational study there are no reported cases of babies born with neural tube defects to women starting dolutegravir later in pregnancy. FDA is investigating this new safety issue and will update the public when FDA has more information.

Dolutegravir is an FDA-approved antiretroviral medicine used in combination with other antiretroviral medicines to treat HIV, the virus that can cause AIDS. Dolutegravir works by blocking integrase, an HIV enzyme, to prevent the virus from multiplying and can reduce the amount of HIV in the body. Stopping dolutegravir without first talking to a prescriber can cause the HIV infection to become worse. Since approval, dolutegravir has been on the US market for 5 years, and is available as a single ingredient product under the brand name Tivicay and as a fixed dose combination tablet with other HIV medicines under the brand names Juluca and Triumeq in US.

Patients should not stop taking dolutegravir without first talking to healthcare professional because stopping the medicine can cause the HIV infection to worsen. In addition:
- If they are already pregnant, stopping

dolutegravir-containing regimen without switching to alternative HIV medicines could cause the amount of virus to increase and spread HIV to their baby.

- If they take a dolutegravir-containing regimen at the time of becoming pregnant and during the first trimester of pregnancy, there is a risk that their baby may develop neural tube defects. Neural tube defects happen early in pregnancy, before many women even know they are pregnant. For this reason, women of childbearing age should talk to their healthcare professional about other non-dolutegravir-containing antiretroviral medicines.
- They should tell healthcare professional if they are pregnant or are planning to become pregnant before they start a dolutegravir-containing regimen. Healthcare professional may discuss other treatment options with them.
- Women of childbearing age who decide to take a dolutegravir-containing regimen should consistently use effective birth control (contraception) while on HIV treatment. Women should talk to their healthcare professionals about an effective birth control method to use while taking a dolutegravir-containing regimen.
- Before they start a dolutegravir-containing regimen they will need a pregnancy test to determine if they are already pregnant.

Healthcare professionals should inform women of childbearing age about the potential risk of neural tube defects when a dolutegravir-containing regimen is used at the time of conception and early in pregnancy. In addition:

- Healthcare professionals should weigh the benefits and the risks of dolutegravir when prescribing antiretroviral medicines to women of childbearing age. Alternative antiretroviral medicines should be considered. Discuss the relative risks and benefits of appropriate alternative antiretroviral therapies.
- If the decision is made to use dolutegravir in women of childbearing age, healthcare professionals should reinforce the consistent use of effective birth control.
- Perform pregnancy testing before initiating a dolutegravir-containing regimen in women of childbearing age to exclude pregnancy.

Ongoing monitoring will continue as part of the observational study in Botswana. Additional birth outcomes are projected from pregnant women who were exposed to dolutegravir at the time of becoming pregnant. FDA will conduct a comprehensive review of the results and any other data that becomes available. FDA will update the public with any new information.

In Hong Kong, there are 2 registered pharmaceutical products containing dolutegravir, namely Tivicay Tablets 50mg (HK-63516) and Triumeq Tablets (HK-64012). Both products are registered by GSK, and are prescription-only medicines. As on 5 June 2018, DH has received 3 cases of ADR related to dolutegravir, but these cases were not related to birth defects.

Related news was issued by EMA on the same date. In view of EMA and US FDA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 21 May 2018. While FDA's review is ongoing, DH will keep vigilant on any further update from EMA, US FDA and other health authorities.

US: Risk of serious and potentially fatal blood disorder prompts FDA action on oral over-the-counter benzocaine products used for teething and mouth pain and prescription local anesthetics

On 23 May 2018, US FDA is warning that over-the-counter (OTC) oral drug products containing benzocaine should not be used to treat infants and children younger than 2 years. FDA is also warning that benzocaine oral drug products should only be used in adults and children 2 years and older if they contain certain warnings on the drug label. These products carry serious risks and provide little to no benefits for treating oral pain, including sore gums in infants due to teething. Benzocaine, a local anesthetic, can cause a condition in which the amount of oxygen carried through the blood is greatly reduced. This condition, called methemoglobinemia, can be life-threatening and result in death.

Due to the significant safety risk of methemoglobinemia, FDA has urged manufacturers that they should stop marketing OTC oral drug products for treating teething in infants and children younger than 2 years. If companies do not comply, FDA will take action to remove these products from the market. FDA has also urged manufacturers of OTC oral drug products containing benzocaine for adults and children 2 years and older to make all the following changes to the labels of their products:

- Adding a warning about methemoglobinemia.
- Adding contraindications, FDA's strongest warnings, directing parents and caregivers not to use the product for teething and not to use in infants and children younger than 2 years.
- Revising the directions to direct parents and caregivers not to use the product in infants and children younger than 2 years.

Benzocaine is a local anesthetic contained in some OTC products for the temporary relief of pain due to minor irritation, soreness, or injury of the mouth and throat. Benzocaine products are marketed as gels, sprays, ointments, solutions, and lozenges.

FDA is also requiring a standardized methemoglobinemia warning to be included in the prescribing information of all prescription local anesthetics. Prescription local anesthetics include articaine, bupivacaine, chloroprocaine, lidocaine, mepivacaine, prilocaine, ropivacaine, and tetracaine.

Consumers using benzocaine products to treat mouth pain should seek medical attention immediately for signs and symptoms of methemoglobinemia. These include pale, gray or blue-colored skin, lips, and nail beds; shortness of breath; fatigue; confusion; headache; lightheadedness; and fast heart rate. Signs and symptoms of methemoglobinemia may appear within minutes to one to two hours after using benzocaine. Symptoms may occur after using benzocaine for the first time, as well as after prior uses.

Healthcare professionals should warn patients of the possibility of methemoglobinemia and advise them of the signs and symptoms when recommending or prescribing local anesthetic products. Some patients are at greater risk for complications related to methemoglobinemia. This includes those with breathing problems such as asthma, bronchitis, or emphysema; heart disease, and the elderly. Healthcare professionals using local anesthetics during medical procedures should take steps to minimize the risk for methemoglobinemia. These include monitoring patients for signs and symptoms suggestive of methemoglobinemia; using co-oximetry when possible; and having resuscitation equipment and medications readily available, including methylene blue.

FDA has been closely monitoring the risk of methemoglobinemia with the use of OTC and prescription local anesthetics and previously communicated about this risk in 2014, 2011, and 2006. FDA estimates that more than 400 cases of benzocaine-associated methemoglobinemia have been reported to FDA or published in the medical literature since 1971. There are likely additional cases about which FDA is unaware.

As part of FDA's continued monitoring of this safety risk, FDA recently evaluated 119 cases of benzocaine-associated methemoglobinemia reported to FDA and identified in the medical literature in the 8½ years between February 2009 and October 2017. FDA has continued to receive cases even after its 2014 communication. Most of the 119 cases were serious and required treatment. Twenty-two cases occurred in patients younger than 18 years, and 11 of these were in children younger than 2 years. Four patients died among the 119 patients, including one infant. FDA also conducted a study comparing the relative ability of the two local anesthetics benzocaine and lidocaine to make methemoglobin. The study showed that benzocaine generated much more methemoglobin than lidocaine in a red blood cell model.

In Hong Kong, there are 14 registered pharmaceutical products containing benzocaine. Amongst these 14 products, 9 products are in oral preparation including 2 products are oral/dental gels and 7 products are lozenges. Regarding the prescription local anesthetics listed in the above FDA's announcement, there are registered prescription products in Hong Kong containing

articaine (7 products), bupivacaine (7 products)/ levobupivacaine (4 products), lidocaine (81 products), mepivacaine (3 products), ropivacaine (3 products) and tetracaine (1 product). Other registered prescription products containing local anesthetics include cocaine (2 products), procaine (4 products) and cinchocaine (9 products). As on 5 June 2018, DH has received 5 cases of ADR related to lidocaine, 1 case related to prilocaine and 2 cases related to cocaine, but these cases were not related to methemoglobinemia.

News related to risk of methemoglobinemia of benzocaine was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 18 and 30. DH issued letters to inform local healthcare professionals to draw their attention on 8 April 2011 and 10 April 2012.

In June 2011 and April 2013, the Registration Committee discussed the matter and decided that the labelling of benzocaine products for topical oral use and all benzocaine products except lozenges preparation should contain information on the risk of methemoglobinemia respectively. In light of the above FDA's updated recommendations, DH issued a letter to inform local healthcare professionals to draw their attention on 24 May 2018 and the matter will be further discussed by the Registration Committee.

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 $30,000 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 accordnance 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.

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