Drug News
藥 物 情 報

Issue Number 132

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in October 2020 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

EU: PRAC reviews a signal with Veklury

On 2 October 2020, the European Medicines Agency (EMA) of the European Union (EU) announced that the EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), has started a review of a safety signal to assess reports of acute kidney injury in some patients with Coronavirus Disease 2019 (COVID-19) taking Veklury (remdesivir).

Veklury has been given a 'conditional marketing authorisation' in the EU for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen, because the benefits to these severely ill patients outweigh the risks of making the medicine available despite having less complete data than normally expected. This means that more evidence is required to be submitted in the post-authorisation phase.

For Veklury, renal toxicity was evaluated at the time of the marketing authorisation application, primarily on the basis of animal studies. It was highlighted in the risk management plan as an important potential risk where further information was needed to better understand the effects of remdesivir on the kidney. Enhanced safety monitoring is in place to pick up reports of unwanted effects and acute kidney injury is being followed as an adverse event of special interest (AESI) in monthly summary safety reports for remdesivir.

At this stage, it has not been determined whether there is a causal relationship between Veklury and the reports of acute kidney injury. The reports form a 'safety signal' - information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation.

Kidney injury can be caused by other factors as well, e.g. diabetes; importantly, COVID-19 is itself known to be a cause. The PRAC will now carefully assess all available data to evaluate if the medicine may have been responsible for the kidney problems and if there is a need to update the existing information for Veklury. Recommendations for the use of this medicine have not changed. The product information in the EU already advises doctors to monitor patients for renal impairment prior to and during treatment and not start treatment in patients with an important decrease in renal function.

The PRAC has started this review based on the results from continuous signal detection work undertaken in EudraVigilance.

The EMA is reviewing any new information that becomes available through monthly summary safety reports (a tool for enhanced safety monitoring), periodic safety update reports and signal detection.

In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet. The EMA will further communicate on the outcome of the PRAC's review.

In Hong Kong, there are 2 registered pharmaceutical products containing remdesivir, namely Veklury Concentrate for Solution for Infusion 100mg/20ml (HK-66765) and Veklury Powder for Concentrate for Solution for Infusion 100mg (HK-66766). Both products are registered by Gilead Sciences Hong Kong Limited. Both medicines are indicated for SARS-CoV-2 infection and conditionally approved for registration for local

unmet medical need under public health emergency based on very limited safety, efficacy and quality data, the benefits of its use outweigh its risk and that there is no other registered pharmaceutical product indicated for use for the treatment of COVID-19. Both products have included safety information related to kidney injury in their product information. As on 5 November 2020, the Department of Health (DH) has received one case of adverse drug reaction (ADR) related to remdesivir but it is not related to kidney injury. In light of the above EMA's announcement, the DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

Singapore: Voluntary withdrawal of Esmya (ulipristal acetate) Tablet 5mg by Zuellig Pharma Pte Ltd

On 9 October 2020, the Health Sciences Authority (HSA) of Singapore announced that Zuellig Pharma Pte Ltd, the product registrant of Esmya (ulipristal acetate) Tablet 5mg, will be voluntarily withdrawing the product from the Singapore market. This is due to concerns with overseas cases of serious liver injury requiring liver transplantation and that it is not possible to identify which patients are most at risk for developing liver injury or to identify measures that could further reduce the risk.

Esmya has been registered for use in Singapore since November 2014, for the pre-operative or intermittent treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age. In March 2020, the HSA had temporarily suspended the sales of Esmya in Singapore as a precautionary measure, due to ongoing concerns of its association with liver injuries reported overseas.

The withdrawal does not affect Ella (ulipristal acetate) Tablet 30mg (Hyphens Pharma Pte Ltd) registered for use as an emergency contraception, as there is no concern about liver injury with this product.

Since 2017, the HSA had been monitoring the safety concern of liver injury with Esmya, following overseas reports of serious liver injuries which had resulted in liver transplantation. The HSA conducted a benefit-risk assessment and implemented additional risk mitigation measures in 2018 to minimise the risk of liver injuries in patients taking Esmya. These measures included prohibiting its use in patients with underlying liver disorders, restricting the use of multiple treatment courses in women who are not eligible for surgery, and increasing the frequency of liver function monitoring. The measures were communicated to healthcare professionals in April 2019 via the company's Dear Healthcare Professional Letter and published in the September 2019 issue of the HSA ADR News Bulletin.

In March 2020, following the report of another overseas case report of serious liver injury with Esmya requiring liver transplantation, the HSA temporarily suspended the sales of Esmya in Singapore as a precautionary measure, while it continued its reassessment of the benefit-risk profile of Esmya for the population in Singapore. A Dear Healthcare Professional Letter was issued for healthcare professionals to review the use of the medicine in their patients and to decide whether a switch to alternative therapies may be appropriate. Healthcare professionals were also advised not to start new patients on Esmya and to monitor existing patients for liver injury for two to four weeks after stopping treatment. As on 9 October 2020, the HSA has not received any reports of serious liver injury related to treatment with Esmya in Singapore.

The sales of Esmya in Singapore has been suspended since March 2020. Healthcare professionals are advised to contact patients under their care who may still be treated with Esmya to:

- Stop Esmya and review alternative treatment options.
- Monitor the liver function of these patients two to four weeks after stopping Esmya treatment.
- Advise patients to monitor for signs and symptoms of liver injury (e.g. dark-coloured urine, yellowing of the skin, excessive tiredness, nausea and vomiting), and to contact their doctors immediately if they develop these signs and symptoms.

In Hong Kong, Esmya (ulipristal acetate) Tablets 5mg (HK-62553) is a pharmaceutical product registered by Orient Europharma Co. Ltd, and is a prescription-only medicine. As on 5 November 2020, the DH has not received any case of ADR related to Esmya.

Related news on the previous review of Esmya was previously issued by various overseas drug regulatory authorities, and was reported in the Drug

News Issue No. 98, 100, 103, 106 and 114. The DH issued a letter to inform local healthcare professionals to draw their attention on the risk of serious liver injury on 12 February 2018. In December 2018, the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the matter, and decided that the sales pack or package insert of the product should include the relevant safety information.

Related news on the recent review of Esmya was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 125 and 131. The DH issued a letter to inform local healthcare professionals to draw their attention on the EMA's recommendation to suspend ulipristal acetate for uterine fibroids on 16 March 2020.

On 20 March 2020, the DH endorsed Orient Europharma Co. Ltd to voluntarily recall Esmya Tablets 5mg (HK-62553) from patients due to the potential risk of liver injury. The recall was reported in the Drug News Issue No. 125 and was completed.

As previously reported, the matter will be discussed by the Registration Committee.

US: FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid

On 15 October 2020, the United States (US) Food and Drug Administration (FDA) announced its warning on use of nonsteroidal anti-inflammatory drugs (NSAIDs) around 20 weeks or later in pregnancy may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid surrounding the baby and possible complications. NSAIDs are commonly used to relieve pain and reduce fevers. They include medicines such as aspirin, ibuprofen, naproxen, diclofenac, and celecoxib. After around 20 weeks of pregnancy, the unborn babies' kidneys produce most of the amniotic fluid, so kidney problems can lead to low levels of this fluid. Amniotic fluid provides a protective cushion and helps the unborn babies' lungs, digestive system, and muscles develop.

Although this safety concern is well known among certain medical specialties, the FDA wanted to communicate its recommendations more widely to educate other healthcare professionals and pregnant women. This issue affects all NSAIDs that are available by prescription and those that can be bought over-the-counter (OTC) without a prescription.

For prescription NSAIDS, the FDA is requiring changes to the prescribing information to describe the risk of kidney problems in unborn babies that result in low amniotic fluid. The FDA is recommending avoiding NSAIDs in pregnant women at 20 weeks or later in pregnancy rather than the 30 weeks currently described in NSAID prescribing information. At around 30 weeks, NSAIDs can cause a problem that may result in heart issues in the unborn baby. If deemed necessary by a healthcare professional, use of NSAIDs between 20 and 30 weeks of pregnancy should be limited to the lowest effective dose for the shortest duration. The changes to the prescribing information also indicate that healthcare professionals should consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours.

The FDA will also update the Drug Facts labels of OTC NSAIDs in the US intended for use in adults. These labels already warn to avoid using NSAIDs during the last 3 months of pregnancy because the medicines may cause problems in the unborn child or complications during delivery. The Drug Facts labels already advise pregnant and breastfeeding women to ask a healthcare professional before using these medicines.

One exception to the above recommendations is the use of the low 81 mg dose of the NSAID aspirin for certain pregnancy-related conditions at any point in pregnancy under the direction of a healthcare professional.

The FDA reviewed the medical literature and cases reported to the FDA for data about low amniotic fluid levels or kidney problems in unborn babies associated with NSAID use during pregnancy. Among the 35 cases of low amniotic fluid levels or kidney problems reported to the FDA through 2017, all were serious. This number includes only cases submitted to the FDA, so there may be additional cases. Two newborns who died had kidney failure and confirmed low amniotic fluid when mothers took NSAIDs while pregnant; three other newborns who died had kidney failure without confirmed low amniotic fluid when mothers took NSAIDs while pregnant. The low amniotic fluid levels started as early as 20 weeks of

pregnancy. In 11 cases where low amniotic fluid levels were detected during pregnancy, the fluid volume returned to normal after the NSAID was stopped. The information from the cases was similar to what was found in the medical literature. In these publications, low amniotic fluid levels were detected with use of NSAIDs for varying amounts of time, ranging from 48 hours to multiple weeks. In most cases, the condition was reversible within 3 to 6 days after stopping the NSAID. In many reports, the condition was reversed when the NSAID was stopped, and it reappeared when the same NSAID was started again.

In Hong Kong, there are registered pharmaceutical products containing nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, diclofenac and celecoxib. As on 5 November 2020, the DH has received ADR related to aspirin (49 cases) and other NSAIDs (38 cases), but these cases are not related to low levels of amniotic fluid. In light of the above FDA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 16 October 2020, and the matter will be discussed by the Registration Committee.

Canada: Benzocaine products should not be used in children under two years of age

On 15 October 2020, Health Canada announced that it is reminding parents and caregivers not to use products containing benzocaine in children under two years of age. Benzocaine products may cause a serious blood condition called methemoglobinemia (MetHb), which reduces the ability of red blood cells to deliver oxygen throughout the body.

OTC products that contain benzocaine are used in children and adults for the temporary relief of minor pain from a variety of conditions, including sore throat, toothache, canker sores, and mouth or gum irritation. In the past, OTC benzocaine products were also used to treat teething pain. Benzocaine products are available in a variety of formulations including gels, sprays, swabs, liquids, lotions, creams and lozenges.

Health Canada previously communicated on this safety issue in November 2006, April 2011 and introduced new labelling requirements in April 2012.

In 2018, Health Canada stopped authorizing benzocaine products for use in children under two years of age. For young children, the serious risk of MetHb is greater than the benefits of benzocaine, especially since children may be unable to communicate that they are experiencing symptoms of MetHb such as weakness, confusion, headache, and/or difficulty breathing.

Most manufacturers of benzocaine products licensed prior to 2018 have added warnings regarding the risk of MetHb and stopped promoting the use of these products in children younger than two years of age. In August 2020, Health Canada issued stop-sales for the few existing benzocaine products that had not updated their labelling. Despite these measures, Health Canada is concerned that healthcare professionals, parents and caregivers may be continuing to recommend or use benzocaine products in this age group given its long history of use as a teething pain reliever.

Information for parents and caregivers:

- Parents and caregivers should not use products that contain benzocaine in children under two years of age.
- Consult with healthcare professional for more details on this new safety information or about alternative options to relieve teething pain and other pain in the mouth.

Information for healthcare professionals:

- Products that contain benzocaine should not be recommended for use in children under two years of age.

In Hong Kong, there are 11 registered pharmaceutical products containing benzocaine. As on 5 November 2020, the DH has not received any case of ADR related to benzocaine.

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, 30 and 103. The DH issued letters to inform local healthcare professionals to draw their attention on 8 April 2011, 10 April 2012 and 24 May 2018. In May 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 February 2019, the Registration Committee further discussed the matter, and decided that the sales pack labels

and/or package inserts of benzocaine products for topical oral use should include the instruction of do not use for teething and in children under 2 years of age. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

UK: Niraparib (Zejula▼): reports of severe hypertension and posterior reversible encephalopathy syndrome (PRES), particularly in early treatment

On 22 October 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced recent reports of onset of severe hypertension (including rare cases of hypertensive crisis) and rare cases of PRES within the first month of niraparib treatment.

A recent European review of the safety data for niraparib identified worldwide reports of patients who developed severe hypertension, including rare cases of hypertensive crisis (may affect up to 1 in 1000 patients), as early as within the first month of treatment with niraparib. The review also identified rare reports of PRES (may affect up to 1 in 1000 patients). Of 5 cases worldwide, 4 patients presented with severe hypertension and 3 reported that PRES occurred during the first month of therapy. Three reports originated from post-marketing sources and 2 from clinical trials.

Hypertension was identified as an important risk with niraparib in clinical trials. The product information for niraparib in the UK had an existing warning for hypertension, including hypertensive crisis, and recommended that blood pressure should be monitored monthly in the first year. Based on the new information identified in the European review, safety warnings have been updated and hypertensive crisis and PRES both added into the product information as rare reactions. The product information has been amended to recommend more frequent blood pressure measurement, especially at the start of treatment. Increase the frequency of blood pressure monitoring to at least weekly for the first 2 months, and then monitor monthly for the first year and periodically thereafter during treatment. For appropriate patients, home blood pressure monitoring can be considered with instruction for patients to contact their healthcare professional in case of rise in blood pressure. Adequate instructions should be provided to patients or caregivers on how to monitor blood pressure at home.

In the UK, up to 30 July 2020, the Yellow Card Scheme received 6 reports associated with hypertension for niraparib. However, limited information is available for the details of the hypertension, including time of onset. No UK Yellow Card reports have been received for PRES associated with niraparib. Caution should be exercised in interpreting these data since there may be under-reporting and use of niraparib in the UK may be relatively low.

Hypertension, including hypertensive crisis, has been reported with the use of niraparib including in the first month of treatment. PRES is a rare, reversible, neurological disorder. The presenting signs and symptoms of PRES include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). The safety of reinitiating niraparib therapy in patients who have previously experienced PRES is not known.

Advice for healthcare professionals:

- There have been reports of severe hypertension (including rare cases of hypertensive crisis) with niraparib, including some with onset in the first month of treatment.
- Rare cases of PRES have also been reported, many associated with hypertension and within the first month of treatment.
- Before treatment, control pre-existing hypertension adequately before starting a patient on niraparib.
- Monitor blood pressure at least weekly for 2 months from initiation and then monthly afterwards for the first year and periodically thereafter during treatment.
- Consider home blood pressure monitoring for appropriate patients; provide adequate training and instruct them to contact their doctor in case of a rise in blood pressure.
- During treatment, manage hypertension with antihypertensives and if necessary, consider treatment interruption and subsequent adjustment of the niraparib dose as advised in product information.
- Discontinue niraparib in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.
- In cases of PRES, discontinue niraparib and treat specific symptoms including

hypertension.

In Hong Kong, Zejula Capsules 100mg (HK-65945) is a pharmaceutical product containing niraparib. The product is registered by Zai Lab (Hong Kong) Limited, and is a prescription-only medicine. As on 5 November 2020, the DH has received 7 cases of ADR related to niraparib, but these cases are not related to severe hypertension and posterior reversible encephalopathy syndrome. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 23 October 2020, and the matter will be discussed by the Registration Committee.

UK: 5-fluorouracil (intravenous), capecitabine, tegafur: DPD testing recommended before initiation to identify patients at increased risk of severe and fatal toxicity

On 22 October 2020, the MHRA announced that patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with these medicines. All patients should be tested for DPD deficiency before initiation to minimise the risk of these reactions.

Fluoropyrimidines are a group of anti-cancer medicines including 5-fluorouracil and its prodrugs capecitabine and tegafur. The DPYD gene encodes DPD, a key enzyme involved in catabolism of 5-fluorouracil. DPD deficiency is most often caused by inherited variants of the DYPD gene. Treatment of patients with DPD deficiency with these medicines increases risk of serious and fatal toxicities.

Complete DPD deficiency is rare (0.01–0.5% of Caucasian people), but partial DPD deficiency is estimated to affect 3–9% of Caucasian people. Most data on the frequency of DPD deficiency are in Caucasian people and rates may differ in other ethnic groups.

A recent European safety review has recommended that, despite uncertainties in the optimal pre-treatment testing methodologies, all patients should undergo testing for DPD deficiency prior to the initiation of these treatments. A letter has been sent to healthcare professionals to inform of these requirements. Safety warnings will also be updated in the Summary of Product Characteristics and Patient Information Leaflets (product information).

Fluorouracil is also available in topical formulations. Due to very low systemic absorption via this route, DPD testing is not required prior to initiation of topical treatment. For topical 5-fluorouracil (5%), if systemic drug toxicity is confirmed or suspected, determination of DPD activity should be considered in line with existing UK product information.

DPD activity is rate limiting in the catabolism of 5-fluorouracil. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidines-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia, and neurotoxicity. DPD-deficiency-related toxicity usually occurs during the first cycle of treatment or after dose increase.

Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated systemically with fluoropyrimidines. Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit the risk of severe toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment and so, in the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Despite negative test results for DPD deficiency, severe toxicity may still occur and patients should be counselled on the benefits and risks of their cancer treatments and provided with the patient information leaflet.

Up to 17 June 2020, the Yellow Card scheme has received 30 reports associated with a fatal outcome that describe a known or suspected DPD deficiency with fluorouracil and capecitabine. These include reports of testing and confirmation of DPD deficiency after patients were treated with capecitabine and developed severe and fatal toxicity. Caution should be exercised in interpreting the Yellow Card data as they may be affected by under-reporting.

The European review considered that pre-treatment genotype testing for mutations of the DPYD gene can identify patients with DPD deficiency. The review described four DPYD variants that can cause complete absence or reduction of DPD enzymatic activity. However, other rare variants

may also be associated with an increased risk of severe or life-threatening toxicity. Data on the frequency of the four DPYD variants in populations other than Caucasian people are limited but their frequency is considered to vary between different ethnic groups.

The European review recommended that phenotyping can also be used to test for DPD deficiency through the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil in plasma. There are uncertainties regarding uracil thresholds to define complete and partial DPD deficiency, however, indicative blood uracil cut-off levels are provided in the amended product information for these medicines.

The European review considered that complementary to DPD deficiency testing before initiation of treatment, therapeutic drug monitoring of 5-fluorouracil may improve clinical outcomes in patients treated with continuous 5-fluorouracil infusions by reducing toxicities and improving efficacy. The target area under the curve (AUC) is between 20 and 30 mg x h/L.

Advice for healthcare professionals:

- Patients with complete or partial DPD deficiency are at increased risk of severe and fatal toxicity during treatment with medicines containing 5-fluorouracil (intravenous), capecitabine, and tegafur.
- DPD deficiency is most often caused by inherited variants of the DYPD gene.
- Test all patients for DPD deficiency before initiation of treatment with these products.
- Ask patients whether they or their family members have history of complete or partial DPD deficiency.
- Do not treat patients with known complete DPD deficiency with these medicines.
- For patients with partial DPD deficiency, consider a reduced starting dose.
- Monitor all patients for toxicity particularly during the first cycle of treatment or after a dose increase.
- Advise patients that despite negative test results for DPD deficiency, severe toxicity may still occur and ensure they have a copy of the patient information leaflet.

In Hong Kong, there are 4 registered pharmaceutical products containing fluorouracil, 24 products containing capecitabine and 4 products containing tegafur. All products are prescription-only medicines. As on 5 November 2020, the DH has received 96 cases of ADR related to fluorouracil, 57 cases related to capecitabine (of which one case is related to dihydropyrimidine dehydrogenase deficiency) and 2 cases related to tegafur.

Related news was previously issued by the EMA, and was reported in the Drug News Issue No. 113, 125 and 126. The DH issued a letter to inform local healthcare professionals to draw their attention on the risk of severe side effects associated with the use of fluorouracil and related medicines (including capecitabine and tegafur) in patients with dihydropyrimidine dehydrogenase deficiency on 18 March 2019. As previously reported, the matter will be discussed by the Registration Committee.

UK: Dolutegravir (Tivicay▼, Triumeq▼, Juluca▼): updated advice on increased risk of neural tube defects

On 22 October 2020, the MHRA announced that updated safety recommendations have been issued as part of the European review evaluating cases of neural tube defects in babies born to mothers who became pregnant while taking the HIV medicine dolutegravir. Evidence collected as more women have given birth while on dolutegravir treatment shows a smaller increased risk than previously thought, almost comparable to other HIV drugs. The previous restrictions against use in pregnancy are no longer in place.

In June 2018, preliminary results from an observational study suggested an increased risk of neural tube defects in infants born to women who took dolutegravir at the time of conception. While a review of this signal was ongoing, the MHRA issued a Drug Safety Update article asking healthcare professional not to prescribe dolutegravir to women who are trying to become pregnant. The product information for dolutegravir in the UK was amended with these recommendations and a letter was sent to healthcare professionals in the UK by the manufacturer.

The study is ongoing and since the article in 2018, additional women were included in the continuing analysis. For a total of 19,361 babies born to women with HIV in Botswana, updated data showed 0.19% (95% CI 0.09–0.40) of babies (7 of 3,591) whose mothers became pregnant while

taking dolutegravir had a neural tube defect, compared with 0.11% (0.07–0.17) of babies (21 of 19,361) whose mothers took other HIV medicines.

The latest review also investigated cases of birth defects in babies born to women who took dolutegravir during pregnancy reported from the Antiretroviral Pregnancy Registry with 660 women exposed to dolutegravir during pregnancy. These data do not indicate an increased risk of major birth defects associated with dolutegravir treatment (absolute risk difference of neural tube defects between dolutegravir and other HIV treatment at conception of 0.08 [95% –CI 0.03 to 0.30]). However, because of the rarity of the neural tube defects, these data are insufficient to completely rule out any risk. Changes will be made to product information advice to reflect the latest review of data.

The review of the study is ongoing. Further advice will be communicated as appropriate as important new information becomes available.

Advice for healthcare professionals:

- Counsel women of childbearing potential about the possible risk of neural tube defects with dolutegravir, including consideration of effective contraceptive measures.
- Discuss the benefits and the risks of continuing treatment with dolutegravir to women who are trying to become pregnant.
- If a pregnancy is confirmed in the first trimester while a patient is on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient, taking into account the gestational age and the critical time period of neural tube defect development.

In Hong Kong, there are 4 registered pharmaceutical products containing dolutegravir, namely Tivicay Tablets 50mg (HK-63516), Triumeq Tablets (HK-64012), Juluca Tablets (HK-66018) and Dovato Tablets (HK-66511). All products are registered by GlaxoSmithKline Limited, and are prescription-only medicines. As on 5 November 2020, the DH has received 3 cases of ADR related to dolutegravir, but these cases are not related to neural tube defects.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 103 and 107. The DH issued a letter to inform local healthcare professionals to draw their attention on the risk of neural tube defects on 21 May 2018. In December 2018, the Registration Committee discussed the matter, and decided that the product insert should include the relevant safety information. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Canada: Brilinta (ticagrelor): Assessing the potential risk of central sleep apnea

On 28 October 2020, Health Canada announced that it reviewed the potential risk of central sleep apnea (CSA) in patients treated with Brilinta (ticagrelor). The safety review was triggered by the publication, in the British Journal of Clinical Pharmacology, of 2 confirmed cases of CSA after starting treatment with Brilinta. CSA is a condition in which breathing repeatedly stops and starts during sleep.

Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases, and published literature. At the time of the review, Health Canada had received 2 Canadian reports of CSA related to Brilinta use. These 2 reports did not have enough information to be assessed. Literature and adverse reaction database searches found 9 case reports (none Canadian, 9 international) that included enough information for review. Four of the 9 cases were from the Canada Vigilance database. In 8 of these reports, a link between Brilinta use and CSA could not be ruled out; 4 reports were found to be probably linked to the use of Brilinta, 4 reports were possibly linked and one report was not likely to be linked. Health Canada also looked at additional information available from 2 studies in published literature. Both studies had a number of weaknesses in their design and reported conflicting results. There is not enough information in these studies to establish a link between Brilinta use and CSA at this time.

Health Canada's review concluded that there may be a link between the use of Brilinta and the risk of CSA. Health Canada will work with the manufacturer to update the Canadian product safety information for Brilinta to add a warning about this potential safety issue.

In Hong Kong, there are 2 registered pharmaceutical products containing ticagrelor,

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namely Brilinta Tab 90mg (HK-61187) and Brilinta Tablets 60mg (HK-64706). Both products are registered by AstraZeneca Hong Kong Ltd, and are prescription-only medicines. As on 5 November 2020, the DH has received 6 cases of ADR related to ticagrelor, but these cases are not related to central sleep apnea. In light of the above Health Canada's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 29 October 2020, and the matter will be discussed by the Registration Committee.

China: Announcement by National Medical Products Administration on amendment of product insert of Ornithine Aspartate Injectables (2020 Issue no. 121)

On 29 October 2020, National Medical Products Administration (NMPA) announced its decision to amend the product insert of ornithine aspartate injectables, including Ornithine Aspartate Injection and Ornithine Aspartate for Injection, in the sections of [adverse reactions], [precautions], [contraindications], [use in pregnancy and lactation], [use in children] and [use in elderly].

Please refer to the following website in NMPA for details:
https://www.nmpa.gov.cn/xxgk/ggtg/ypshmshxdgg/20201029151116103.html

In Hong Kong, there is one registered pharmaceutical product which is an injection containing ornithine aspartate, namely Hepa-Merz Infusion Conc for IV Infusion (HK-26079). The product is registered by Jacobson Medical (Hong Kong) Ltd (Jacobson), and is a prescription-only medicine. As on 5 November 2020, the DH has not received any case of ADR related to ornithine aspartate. The above revised contents of the product insert, including contraindications, safety information in pregnancy and lactation, and side effects of gastrointestinal disorders, are similar to those contained in the current product insert. Jacobson has already submitted application for update of the product insert to include side effects such as hypersensitivity and anaphylactic reaction. In view of the above NMPA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 30 October 2020. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Drug Recall

DH endorsed recall of Solcoseryl Eye Gel (HK-21628)

On 7 October 2020, the DH endorsed a licensed drug wholesaler, A. Menarini Hong Kong Limited (A. Menarini), to recall Solcoseryl Eye Gel (HK-21628), from the market as a precautionary measure because the sterility of the product cannot be guaranteed.

The DH received notification from overseas health authorities that the manufacturer of the product failed to comply with the Good Manufacturing Practice in their sterile manufacturing operations, and the sterility of their sterile medicinal products cannot be guaranteed. As a precautionary measure, A. Menarini voluntarily recalled the product from the market.

The above product, containing calf blood derivatives, is used for the treatment of disorders or injuries of the cornea or conjunctiva of the eye. According to the wholesaler, the product has been supplied to the Hospital Authority, the DH, private hospitals, local private doctors, pharmacies and medicine stores.

Patients who are using the above product should stop using it, and should seek advice from their healthcare professionals as soon as possible for appropriate arrangements.

As on 5 November 2020, the DH has not received any adverse reaction reports in connection with the product. Press release was posted on the Drug Office website on 7 October 2020 to alert the public of the product recall.

DH endorsed batch recall of Metformin Denk 850 Tablets 850mg (HK-49776)

On 9 October 2020, the DH endorsed a licensed drug wholesaler, Star Medical Supplies Ltd (Star Medical), to recall one batch (Batch Number: 21334) of Metformin Denk 850 Tablets 850mg (HK-49776) from the market as a precautionary measure due to the possible presence of an impurity in the product.

The DH received notification from an overseas

Drug Recall

drug regulatory authority that the aforementioned batch of Metformin Denk 850 Tablets 850mg was found to contain an impurity, *N*-nitrosodimethylamine (NDMA). As a precautionary measure, Star Medical voluntarily recalled the affected batch from the market.

NDMA is classified as a probable human carcinogen based on results from laboratory tests. Overseas drug regulatory authorities have been reviewing the safety impact of NDMA found in some medicinal products including metformin.

The above product, containing metformin, is a prescription medicine used for the treatment of diabetes mellitus. According to Star Medical, the product has been supplied to local private doctors and pharmacies.

Patients who are taking the above product should not stop taking the medicine, and should seek advice from their healthcare professionals as soon as possible for appropriate arrangements.

As on 5 November 2020, the DH has not received any adverse reaction reports in connection with the product. Press release was posted on the Drug Office website on 9 October 2020 to alert the public of the product recall.

Overall situation related to detection of NDMA in metformin

As on 5 November 2020 in Hong Kong, there are 125 registered pharmaceutical products containing metformin. All products are prescription-only medicines.

Related news on the detection of NDMA in metformin products was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 122 and 124. The DH issued a letter to inform local healthcare professionals to draw their attention on 6 December 2019. The DH has contacted the certificate holders of all registered metformin products for follow up on the local impact of the issue, and collected samples of metformin-containing products in the local market for analysis. When there are any health risks identified and posed to the public, a press statement will be issued as soon as possible. Please find update information at Drug Office's website (www.drugoffice.gov.hk). The following is the main content of the press statement issued previously:

- On 11 March 2020, the DH endorsed a licensed wholesale dealer, the International Medical Company Ltd, to recall 3 batches of Metformin-Teva 500mg Tablets (HK-60334) (batch number: 16532717, 16532817 and 16532917) from the market due to the potential presence of NDMA in the product.
- On 22 July 2020, the DH endorsed licensed wholesaler dealers Suntol Medical Ltd and Hovid Limited to recall Glucofit Extended-Release Tablets 500mg (HK-64640) and Diabetmin XR Extended-Release Tablets 500mg (HK-63333) respectively.
- On 24 August 2020, the DH endorsed licensed wholesaler dealer Suntol Medical Ltd to recall Glucofit Film Coated Tablets 500mg (HK-64639).

The above recalls were reported in the Drug News Issue No. 125, 129 and 130. As on 5 November 2020, the DH has received 17 cases of ADR related to metformin. None of them is concluded to be related to the presence of NDMA. The DH will remain vigilant on the development of the issue and any safety update of the drug issued by overseas drug regulatory authorities for consideration of any action deemed necessary.

Patients who are taking metformin-containing products should not stop taking the medicines, but should seek advice from their healthcare professionals for proper arrangement.

Drug Incident

Public urged not to buy or consume unlabelled slimming products with controlled ingredients

On 30 October 2020, the DH appealed to the public not to buy or consume unlabelled slimming products that may contain controlled medicine ingredients.

Acting upon a public complaint, a local Internet seller was found offering for sale various unlabelled slimming products claiming to be obtained from overseas. Samples of the products were purchased via a social media platform for analysis. Test results from the Government Laboratory revealed that five products contained Part 1 poisons including hydrochlorothiazide,

propranolol and fluoxetine.

Hydrochlorothiazide and propranolol are used for the treatment of hypertension. Side effects of hydrochlorothiazine include low blood pressure and electrolytes imbalance, while those of propranolol include abdominal discomfort, confusion, depression and dizziness. Fluoxetine is used for treatment of mood disorders and may cause hallucinations and insomnia.

Members of the public who have purchased the above product should stop consuming it immediately. They should consult healthcare professionals for advice if feeling unwell after consumption.

Weight control should be achieved through a balanced diet and appropriate exercise. The public should consult healthcare professionals before using any medication for weight control. They may visit the website of the Drug Office of the DH for "Health messages on overweight problem and slimming products" and "Information on slimming products with undeclared Western drug ingredients" for more information.

Press release was posted on the Drug Office website on 30 October 2020 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 $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 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.

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: ***Undesirable Medical Advertisements and Adverse Drug Reaction Unit,***
Drug Office, Department of Health,
Suites 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.