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 December 2017 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: EMA starts review of Esmya for uterine fibroids - Review triggered by cases of liver injury

On 1 December 2017, the European Medicines Agency (EMA) of European Union (EU) announced that EMA has started a review of the medicine Esmya (ulipristal acetate) used to treat uterine fibroids (non-cancerous tumours of the womb). This follows four reports of serious liver injury, three of which ended in liver transplantation, in patients treated with the medicine.

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has made an initial assessment of the cases of liver injury and considered that Esmya could be the cause.

Given the seriousness of the observed liver injury and its possible link to the medicine, a more in depth review is warranted.

PRAC will now evaluate all available data and determine whether there are any implications for the use of Esmya.

While the review is ongoing, patients should contact their doctor if they have any questions or concerns about their treatment.

Ulipristal acetate is also the active substance of a single-dose medicine authorised for emergency contraception, ellaOne. No cases of serious liver injury have been reported with ellaOne and there are no concerns with this medicine at this time.

In Hong Kong, Esmya Tablets 5mg (HK-62553) is a pharmaceutical product registered by Orient Europharma Co. Ltd. and is a prescription-only medicine. As on 5 January 2018, the Department of Health (DH) has not received any case of adverse drug reaction (ADR) related to Esmya. In view of the EU PRAC's review is ongoing, DH will keep vigilant on the result and against any safety updates of the drug.

Canada: Health Canada strengthens safety information for all opioid drugs

On 8 December 2017, Health Canada announced that, as part of the Government's action to reduce the harms of opioids, Health Canada held a Scientific Advisory Panel on Opioid Use and Contraindications to consider whether the current contraindications for opioid use are sufficient, or whether labelling updates and other actions may be needed to reduce risks to Canadians. The Panel's recommendations, which also consider the recently published Canadian Guideline for Opioids for Chronic Non-Cancer Pain, can be found in the following website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/scientific-expert-advisory-panels/opioid-use-contraindications/record-proceedings-2017-03-24.html.

After thoroughly assessing the Panel's recommendations, Health Canada is working with manufacturers to update the Canadian labelling of all prescription opioid products. Labelling updates include:

- Recommendation for a daily opioid threshold dose for the management of chronic non-cancer, non-palliative pain (which aims to reduce risks of adverse events and overdoses associated with taking higher doses of opioids).

- Recommendation to limit the quantity of opioids prescribed for acute pain (which aims to reduce the duration of use and associated risks of developing dependence and substance use disorder).
- Clarification of warnings, including those for special populations such as pregnant women and patients with a history of dependence or substance use disorder.

Health Canada wants to ensure that opioid medications are available to all patients who need them, while limiting the potential for unwanted harms. While prescription opioid labels are being updated to include enhanced information about product risks, they continue to allow for physician discretion to adequately treat individual patients. For example, a recommendation may be presented in the dosing and administration section of the labelling, rather than as a contraindication, so that physicians can continue to consider the relative risks and benefits for individual patients in making their treatment decisions.

In Hong Kong, opioid medicines are considered as pharmaceutical products. As on 5 January 2018, DH has received 6 cases of ADR related to dextropropoxyphene, morphine, pethidine and tramadol. DH will keep vigilant on the safety update regarding opioid medicines by other overseas drug regulatory authorities.

Singapore: Ofev® (nintedanib) - Risk of severe liver injury in patients with idiopathic pulmonary fibrosis (IPF)

On 11 December 2017, the Health Sciences Authority (HSA) of Singapore announced that Boehringer Ingelheim would like to inform healthcare professionals that post-marketing cases of drug-induced liver injury (DILI) have been reported in patients with IPF treated with Ofev®. Majority of the hepatic events occurred within the first three months of Ofev® initiation. Therefore, transaminases and bilirubin levels should be investigated upon initiation of treatment, at regular intervals during the first three months of treatment and periodically thereafter (e.g. at each patient visit) or as clinically indicated. Boehringer Ingelheim is working with HSA to update the package insert for Ofev® in Singapore to reflect the new information on the cases of DILI and to provide further guidance on the monitoring schedule of the liver function.

In Hong Kong, there are 4 registered pharmaceutical products containing nintedanib, namely Vargatef Capsules 100mg (HK-64395), Vargatef Capsules 150mg (HK-64396), Ofev Capsules 100mg (HK-64604) and Ofev Capsules 150mg (HK-64605). All products are registered by Boehringer Ingelheim (HK) Ltd, and are prescription-only medicines. As on 5 January 2018, DH has received 3 cases of ADR related to nintedanib, but none of them was related to liver injury. DH issued a letter to inform local healthcare professionals to draw their attention on the above safety information on 13 December 2017. DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

UK: Fingolimod (Gilenya▼): updated advice about risk of cancers and serious infections

On 14 December 2017, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that fingolimod has an immunosuppressive effect. A recent routine EU review recommended strengthened warnings for malignancies including skin cancers and lymphoma and serious opportunistic infections.

Regarding the risk of malignancy, basal cell carcinoma and lymphoma were already known to occur in patients taking fingolimod and annual skin screening was advised. The review identified post-marketing reports of T-cell lymphoma (mostly cutaneous) and other types of skin cancer, including malignant melanoma (uncommon; post-marketing frequency less than 1 in 100 patients), squamous cell carcinoma (rare; less than 1 in 1,000), Kaposi sarcoma (very rare; less than 1 in 10,000), and Merkel cell carcinoma (unknown frequency).

Regarding the risk of fatal fungal infections and reports of progressive multifocal leukoencephalopathy (PML), analysis of post-marketing reports suggest a higher risk of serious

infections, including fatal fungal infections, than clinical trial data predicted. Although the exact frequency of these infections is not known, vigilance for serious opportunistic infections is recommended. The routine review identified 54 reports of opportunistic systemic fungal infections, including 9 fatal cases of cryptococcal meningitis, over 397,764 patient-years of exposure since marketing.

In April 2016, MHRA informed public about reports of PML in patients taking fingolimod. Worldwide, PML has been reported in 79 patients taking fingolimod post-marketing, including 22 cases attributable to fingolimod.

Healthcare professionals are advised to:
- Re-assess the benefit-risk balance of fingolimod therapy in individual patients, particularly those with additional risk factors for malignancy.
- Examine all patients for skin lesions before starting fingolimod and closely monitor for skin cancers at least every 6 to 12 months.
- Advise patients to avoid exposure to UV radiation (including sunlight and phototherapy) and seek urgent medical advice if they notice any skin lesions.
- Advise patients to seek urgent medical attention if they develop any symptoms or signs consistent with an infection, including up to 2 months after the end of fingolimod therapy.
- Report all suspected ADR with fingolimod, including after discontinuation.

In Hong Kong, Gilenya Hard Capsules 0.5mg (HK-61192) is a pharmaceutical product containing fingolimod which is registered by Novartis Pharmaceuticals (HK) Limited (Novartis), and is a prescription-only medicine. As on 5 January 2018, DH has received one case of ADR related to fingolimod, but it was not related to cancers and infections.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 46, 70, 71 and 78. DH issued letters to inform local healthcare professionals to draw their attention related to risk of cancers and serious infections on 5 August 2015, 2 October 2015 and 19 April 2016. Novartis has submitted application to update the package insert of the product, the application is being reviewed and the updated package insert will contain the new warnings in the above MHRA's announcement including skin cancers.

UK: Fingolimod (Gilenya▼): new contraindications in relation to cardiac risk

On 14 December 2017, MHRA announced that fingolimod can cause transient bradycardia and second-degree or third-degree atrioventricular (AV) block in early treatment.

In January 2013, MHRA highlighted the need for cardiac monitoring after the first dose of fingolimod. However, some patients can have persistent bradycardia, which can increase the risk of serious cardiac arrhythmias.

A recent routine EU review identified 44 post-marketing reports of serious ventricular tachyarrhythmia and 6 reports of sudden death worldwide in patients taking fingolimod up to the end of February 2017. Cumulative exposure to fingolimod post-marketing was estimated to be 397,764 patient-years. The routine EU review recommended that warnings against the use of fingolimod in patients with underlying cardiac disorders should be strengthened to contraindications.

Healthcare professionals are advised that:
- Fingolimod can cause serious ventricular arrhythmias, particularly in the first year of use.
- Fingolimod is now contraindicated in patients with myocardial infarction or unstable angina, cerebrovascular disease (transient ischaemic attacks, stroke), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure in the previous 6 months, severe cardiac arrhythmias requiring treatment with class Ia (e.g. quinidine, procainamide, disopyramide) and class III (potassium-channel blockers – e.g. amiodarone, sotalol, ibutilide, dofetilide) antiarrhythmic drugs, second-degree Mobitz type II AV block or third-degree AV block, or sick-sinus syndrome, if they do not have a pacemaker, pre-treatment QT intervals ≥500 milliseconds.
- All suspected ADR with fingolimod should be

reported.

In Hong Kong, Gilenya Hard Capsules 0.5mg (HK-61192) is a pharmaceutical product containing fingolimod which is registered by Novartis, and is a prescription-only medicine. As on 5 January 2018, DH has received one case of ADR related to fingolimod, which is related to bradycardia.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 30. DH issued letters to inform local healthcare professionals to draw their attention about cardiac risk on 23 April 2012 and 15 December 2017. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee).

UK: Radium-223 dichloride (Xofigo▼): do not use in combination with abiraterone and prednisone/prednisolone, following clinical trial signal of increased risk of death and fractures

On 14 December 2017, MHRA announced that preliminary data from a randomised, double-blind, placebo-controlled study showed an increased incidence of deaths (27% versus 20%) and fractures (24% versus 7%) among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone (n=401) compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone (n=405). This study in asymptomatic or mildly symptomatic chemotherapy-naive patients with bone-predominant metastatic castration-resistant prostate cancer was unblinded early based on an Independent Data Monitoring Committee recommendation.

Until full analysis of the results is completed, do not use radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone to treat metastatic castration-resistant prostate cancer. Further advice will be communicated as appropriate at the end of the review.

In Hong Kong, Xofigo Solution for Injection 1100 kBq/mL (HK-64332) containing radium-223 dichloride and Zytiga Tablets 250mg (HK-61370) containing abiraterone acetate are pharmaceutical products registered by Bayer Healthcare Ltd and Johnson & Johnson (Hong Kong) Ltd. respectively. Both products are prescription-only medicines. As on 5 January 2018, DH has received 10 cases of ADR related to Xofigo and 3 cases of ADR related to Zytiga, but none of them are related to death and fractures.

The above clinical trial has not been conducted in Hong Kong. DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

EU: Modified-release paracetamol-containing products to be suspended from EU market

On 15 December 2017, EMA announced that EMA's Co-ordination Group for Mutual Recognition and Decentralised procedures – Human (CMDh) has endorsed by majority a EMA recommendation to suspend marketing of modified- or prolonged-release products containing paracetamol (designed to release paracetamol slowly over a longer period than the usual immediate-release products). The recommendation was made by the Agency's experts in medicines safety, PRAC.

CMDh agreed with EMA's advice that the advantages of a longer-acting product did not outweigh the complications of managing an overdose of the medicine, since the treatment procedures for immediate-release products are not appropriate for modified-release paracetamol. In many cases, it may not be known whether an overdose of paracetamol involves immediate-release or modified-release products, making it difficult to decide how the overdose should be managed.

CMDh noted the PRAC conclusion that practical measures to sufficiently reduce the risk to patients had not been identified. Furthermore, it had not proved possible to agree a feasible and standardised way to adapt the management of overdose across

EU to cover both immediate- and modified-release paracetamol products. CMDh therefore endorsed the PRAC recommendation that the marketing authorisations for medicines containing modified-release paracetamol, alone or combined with the opioid medicine tramadol, should be suspended.

The medicines will remain suspended unless the companies that hold the marketing authorisations can provide evidence of appropriate and practical EU-wide measures to help prevent overdose with these products and adequately reduce its risks.

Immediate-release paracetamol products, which are not affected by this review, will continue to be available as before.

Because the CMDh decision was agreed by majority vote, it will now be sent to the European Commission which will issue a final legally binding decision valid throughout EU.

Healthcare professionals are advised of the followings:

- Modified-release paracetamol (alone or combined with tramadol) is being removed from the EU market since overdoses with modified-release paracetamol products can be unpredictable in their pharmacokinetics, and complex to manage.
- The established treatment guidelines for paracetamol overdose are based on the immediate-release products and may not be effective for treatment of overdoses with modified-release paracetamol.
- There are no issues with modified-release paracetamol preparations when used in accordance with their product information. Patients can safely continue treatment in the approved indication and doses with any remaining supply. Prescribers should discuss switching to an appropriate alternative if necessary once patients' supply runs out.
- Until modified-release products have been removed from the market, adaptations of the standard protocol for paracetamol overdose should be considered. Although this should be determined at local level in consultation with local Poison Information Centres, the following general guidance may be helpful unless local guidelines have already been adapted or already recommend a more conservative approach:
  - where overdose with ≥10 g of paracetamol (or ≥150 mg/kg body weight in children) is known or suspected, or where dose is unknown, treatment with antidote (N-acetylcysteine, NAC) should be started immediately regardless of the initial serum paracetamol level, since serum paracetamol level after acute overdose with modified-release products may peak up to 24 hours after ingestion;
  - where <10 g of paracetamol has been ingested and time since ingestion is known, multiple serum paracetamol samples should be taken at suitable intervals (e.g. 4, 6, and 8 hours after ingestion). Additional samples should be considered if serum paracetamol concentrations are not declining to low levels. If serum paracetamol levels exceed the treatment nomogram at any time point, treatment with antidote (NAC) is indicated;
  - if time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, it is recommended that treatment with antidote (NAC) should be initiated without waiting for serum paracetamol concentrations to be available;
  - if NAC treatment has been initiated, it should be prolonged beyond the first 21-hour NAC course if paracetamol level remains above the limit of detection (or greater than 10 mg/L) or if alanine aminotransferase (ALT) is increasing (greater than 100 U/L), and should be continued until paracetamol is below the limit of detection (or 10 mg/L) or if ALT is falling below 100 U/L;
  - antidote should be dosed as recommended by the local Poison Information Centre.

In Hong Kong, there are 7 registered pharmaceutical products containing paracetamol in modified-/prolonged-release dose form and they belong to non-prescription medicines. The 7 products include Clariflu Sustained Release Tab (HK-47205) which is registered by Bayer Healthcare Ltd; Panadol Joint Extended Release

Caplet 665mg (HK-59436), Panadol Long Lasting Tab 665mg (HK-51314), Panadol Extend Tab 665mg (HK-51316) and Panadol Extend Tab 665mg (Ireland) (HK-52683) which are registered by GlaxoSmithKline Consumer Healthcare (Hong Kong) Limited; Xykaa Extend Prolonged Release Tablet 650mg (HK-61400) which is registered by Evercare Pharmaceutical Co. Ltd.; and Ensid-ER Extended Release Tablet 650mg (HK-62272) which is registered by LSB (HK) Ltd.

As on 5 January 2018, DH has received 11 ADR cases related to overdose/ liver injury after taking products containing paracetamol. In February 2011, the Registration Committee had discussed the risk of liver toxicity related to paracetamol, and decided that the sales packs of paracetamol products should include warnings on the potential risks of liver toxicity and damage, and advices against using more than the recommended dose and against using more than one product containing paracetamol. Related news of EMA to review modified-release paracetamol was reported in the Drug News Issue No. 81. DH issued a letter to inform local healthcare professionals to draw their attention on the EMA recommendation on 4 September 2017.

As previously reported, the matter with the above information announced by EMA will be discussed by the Registration Committee.

EU: Updated recommendations for contraception in men and women taking mycophenolate medicines

On 15 December 2017, EMA has updated recommendations for contraception in men and women taking mycophenolate medicines which are used to prevent rejection of transplanted organs.

Mycophenolate medicines are known to increase the risk of malformations and miscarriages during pregnancy if the fetus is exposed to them in the womb.

EMA has concluded that current evidence does not indicate a risk of malformations or miscarriages when the father has taken mycophenolate, although the risk of genotoxicity cannot be completely ruled out.

For male patients, EMA now recommends that either the male patient or his female partner use reliable contraception during mycophenolate treatment and for at least 90 days after stopping treatment.

The previous recommendation that male patients should use condoms in addition to their female partners using a highly effective method of contraception has now been removed as this does not reflect the level of risk.

For female patients, the risk is unchanged. These medicines must not be used in pregnant women unless there are no suitable alternatives to prevent transplant rejection. In addition, female patients who can become pregnant must use at least one reliable form of contraception before, during and for 6 weeks after stopping treatment. Two forms of contraception are preferred but no longer mandatory.

The updated recommendations follow a periodic review of mycophenolate medicines by EMA's PRAC, which considered the available clinical and non-clinical data. The recommendations have now been adopted by the Committee for Medicinal Products for Human Use.

Healthcare professionals and patients are advised of the followings:

- Recommendations to manage the risk of malformations or miscarriages following treatment with mycophenolate have been updated.
- Male patients or their untreated female partner must use reliable contraception during mycophenolate treatment and for at least 90 days after stopping treatment. (It is no longer required that they both use contraception.)
- Female patients who can get pregnant must use at least one reliable form of contraception before, during and for 6 weeks after stopping treatment. Two forms of contraception are preferred but no longer mandatory.
- Patients and healthcare professionals are reminded that mycophenolate medicines must

never be used in pregnant women except in those instances where there are no suitable alternatives to prevent organ rejection.
- Patients who have any questions should speak to their doctor.

In Hong Kong, there are 27 registered pharmaceutical products containing mycophenolate mofetil or mycophenolic acid. All products are prescription-only medicines. News on teratogenic risk of mycophenolic acid related drugs was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 72. DH issued a letter to inform local healthcare professionals to draw their attention on the advice to prevent pregnancy when using the products on 26 October 2015. As on 5 January 2018, DH has received 24 cases of ADR in connection with mycophenolate mofetil or mycophenolic acid, and one of them was related to missed abortion after taking the drug.

In December 2016, the Registration Committee discussed the teratogenic risk of mycophenolic acid and related drugs, and decided that the sales pack and/or package insert of the products should be updated to include the relevant safety information on teratogenic risk and pregnancy prevention advice endorsed by other overseas drug regulatory authorities including EMA.

In view of the above EMA's recommendations, DH will continue to remain vigilant on any new safety update by other overseas drug regulatory authorities regarding mycophenolic acid and related drugs.

US: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings

On 19 December 2017, the United States (US) Food and Drug Administration (FDA) announced that FDA is requiring a new class warning and other safety measures for all GBCAs for magnetic resonance imaging (MRI) concerning gadolinium remaining in patients' bodies, including the brain, for months to years after receiving these drugs. Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and FDA has concluded that the benefit of all approved GBCAs continues to outweigh any potential risks.

However, after additional review and consultation with the Medical Imaging Drugs Advisory Committee, FDA is requiring several actions to alert healthcare professionals and patients about gadolinium retention after an MRI using a GBCA, and actions that can help minimize problems. These include requiring a new patient Medication Guide, providing educational information that every patient will be asked to read before receiving a GBCA. FDA is also requiring manufacturers of GBCAs to conduct human and animal studies to further assess the safety of these contrast agents.

Healthcare professionals should consider the retention characteristics of each agent when choosing a GBCA for patients who may be at higher risk for gadolinium retention. These patients include those requiring multiple lifetime doses, pregnant women, children, and patients with inflammatory conditions. Minimize repeated GBCA imaging studies when possible, particularly closely spaced MRI studies. However, do not avoid or defer necessary GBCA MRI scans. Patients, parents, and caregivers in US should carefully read the new patient Medication Guide that will be given to them before receiving a GBCA.

As on 19 December 2017, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis that occurs in a small subgroup of patients with pre-existing kidney failure. FDA has also received reports of adverse events involving multiple organ systems in patients with normal kidney function. A causal association between these adverse events and gadolinium retention could not be established.

FDA is continuing to assess the health effects of gadolinium retention in the body and will update the public when new information becomes available. FDA is requiring the following specific changes to the labeling of all GBCAs:
- A Warning and Precaution.
- Changes related to gadolinium retention in the

Adverse Reactions, Pregnancy, Clinical Pharmacology, and Patient Instructions sections.

In Hong Kong, there are 8 registered pharmaceutical products which are GBCAs, 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 and 93. DH issued a letter to inform local healthcare professionals to draw their attention on 24 July 2017. As on 5 January 2018, DH has received 7 cases of ADR in connection with GBCAs: 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. As previously reported, the matter will be discussed by the Registration Committee.

US: Long-Acting Beta agonists (LABAs) and Inhaled Corticosteroids (ICS): Boxed Warning about asthma-related death removed

On 20 December 2017, US FDA announced that FDA's most prominent warning, the Boxed Warning, about asthma-related death has been removed from the drug labels of medicines that contain both an ICS and LABA.

A FDA review of four large clinical safety trials shows that treating asthma with LABAs in combination with ICS does not result in significantly more serious asthma-related side effects than treatment with ICS alone. A description of the four trials is also included in the Warnings and Precautions section of the drug labels in US. These trials showed that LABAs, when used with ICS, did not significantly increase the risk of asthma-related hospitalizations, the need to insert a breathing tube known as intubation, or asthma-related deaths, compared to ICS alone.

In 2011, FDA required the drug companies manufacturing fixed-dose combination drugs containing an ICS and LABA (GlaxoSmithKline, Merck, Astra Zeneca) to conduct several large, 26-week, randomized, double-blind, active-controlled clinical safety trials to evaluate the risk of serious asthma-related events when LABAs were used in fixed-dose combination with an ICS compared to ICS alone in patients with asthma. FDA reviewed the results of four trials involving 41,297 patients. The results demonstrate that the use of ICS/LABA in fixed-dose combination does not result in a significant increase in the risk of serious asthma-related events compared to ICS alone. The results of subgroup analyses for gender, adolescents 12-18 years, and African Americans are consistent with the primary endpoint results.

The four trials also assessed efficacy of the ICS/LABA products. The primary efficacy endpoint was asthma exacerbation, defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days, or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. The results showed that the ICS/LABA combination reduced asthma exacerbations compared to ICS alone, noting that the majority of these exacerbations were those that required at least 3 days of systemic corticosteroids. This efficacy information has been added to the Clinical Studies section of the ICS/LABA drug labels in US.

In Hong Kong, there are 26 registered pharmaceutical products containing both an ICS and LABA, and all are prescription-only medicines. Related news was previously issued by FDA, and was reported in the Drug News Issue No. 5. DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

Canada: New warnings regarding the use of certain sedative and anesthetic drugs during pregnancy and in early childhood

On 22 December 2017, Health Canada announced that new safety warnings will be added to the product safety information of the following sedative and anesthetic drugs when they are used in early childhood and during pregnancy: Diprivan (propofol), Ketalar (ketamine), Sevorane (sevoflurane), Suprane (desflurane), Forane/ Isoflurane USP (isoflurane), Ativan (lorazepam), midazolam, phenobarbital and thiopental.

Two reviews have been conducted to assess the potential risk of adverse effects on the development of children's brains when certain sedative and anesthetic drugs are used in pregnancy or in early childhood.

The safety review for Diprivan (propofol), Ketalar (ketamine), Sevorane (sevoflurane), Suprane (desflurane) and Forane/Isoflurane USP (isoflurane) concluded that repeated or lengthy use of these drugs (more than 3 hours) during pregnancy or in children up to approximately 3 years of age may potentially lead to adverse effects on the development of children's brains, such as intellectual and learning disabilities, and problems with communication and movement.

The safety review for benzodiazepines (Ativan [lorazepam] and midazolam) and barbiturates (phenobarbital and thiopental) concluded that there is limited evidence linking the use of these drugs by pregnant women and young children to adverse effects on the development of children's brains. However, it is important to note that many of these sedatives may often be used in combination with other intravenous and inhaled anesthetics, which were found to have a risk of adverse effects related to the functioning of the brain.

Health Canada will also look into working with the Drug Safety and Effectiveness Network to further study the link between the use of sedative and anesthetic drugs and the development of the brain.

Health professionals and patients should weigh the risks and benefits when making any decisions on the necessity and timing of a procedure. Pregnant women, parents and caregivers should discuss any questions or concerns about the safety of sedatives, general anesthesia and the necessity of a procedure with their healthcare professional. Side effects associated with these drugs should be reported.

In Hong Kong, there are 57 registered pharmaceutical products containing general anaesthetics and sedation drugs listed in US FDA announcement in December 2016 and this Health Canada announcement, including desflurane (1 product), etomidate (1), isoflurane (5), ketamine (5), lorazepam (15), midazolam (11), pentobarbital (1), propofol (6), sevoflurane (4) and phenobarbital (8). Related news was previously issued by FDA and Health Canada, and was reported in the Drug News Issue No. 86. DH issued a letter to inform local healthcare professionals to draw their attention on 15 December 2016. As on 5 January 2018, DH has received 7 cases of ADR related to ketamine, 1 case related to lorazepam, 21 cases related to midazolam and 1 case related to phenobarbital, but none of them are related to brain development of children when used during pregnancy or in early childhood. As previously reported, the matter will be discussed by the Registration Committee.

Singapore: Risk of hepatitis B virus (HBV) reactivation with ibrutinib

On 27 December 2017, HSA announced the potential risk of HBV reactivation associated with ibrutinib treatment. This risk was identified by EMA following its review of overseas cases of HBV reactivation in patients who received treatment with ibrutinib.

EMA's PRAC conducted a routine review examining the safety profile of ibrutinib, which identified cases of HBV reactivation in ibrutinib-treated patients. This cumulative review took into consideration available data from clinical trials, scientific literature, as well as postmarketing ADR reports of HBV reactivation in patients receiving ibrutinib treatment. EMA's review of cumulative data available till November 2016 identified eight

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cases of HBV reactivation in which the role of ibrutinib was considered possible or probable. In other cases, the role of ibrutinib in the onset of HBV reactivation could not be clearly established due to confounding by prior or concomitant treatment regimens known to be associated with the development of viral reactivation. The remaining cases had insufficient information to allow for meaningful causality assessment. None of the cases of HBV reactivation had led to fulminant liver failure requiring liver transplantation. However, there was one report with a fatal outcome, which was attributed to HBV reactivation and concurrent metastatic melanoma of the liver, lung and spleen.

Based on review of the available information, EMA's PRAC concluded in June 2017 that the benefit-risk balance of ibrutinib in relation to its approved indications remained unchanged. However, PRAC recommended that healthcare professionals establish the HBV status of patients prior to initiating treatment with ibrutinib. In patients with positive hepatitis B serology, consultation with a hepatic disease expert is recommended before initiating treatment with ibrutinib. PRAC also advised that patients with positive hepatitis B serology who require ibrutinib be monitored and managed according to local medical standards of care, so as to minimise the risk of HBV reactivation. The EU product information for ibrutinib would also be updated to include warnings on the risk of HBV reactivation and to include HBV reactivation as an uncommon adverse reaction.

HSA has not received any adverse reaction report of HBV reactivation in patients receiving treatment with ibrutinib in Singapore. The Singapore package insert for ibrutinib (Imbruvica®) will be updated to include safety information regarding the risk of HBV reactivation. In view of the higher prevalence of hepatitis B in Singapore than in Europe, and the potentially serious outcomes caused by HBV reactivation in immunosuppressed patients, healthcare professionals should ensure that HBV status is established before initiating treatment with ibrutinib. They are also advised to closely monitor patients with positive hepatitis B serology who require ibrutinib and institute appropriate therapy as indicated to minimise the risk of hepatitis B reactivation.

In Hong Kong, there are 2 pharmaceutical products containing ibrutinib, namely Imbruvica Capsules 140mg (HK-64088) and Imbruvica Capsules 140mg (HK-65397). Both products are registered by Johnson & Johnson (Hong Kong) Ltd. (Johnson HK), and are prescription-only medicines. As on 5 January 2018, DH has received 7 cases of ADR related to ibrutinib, but these cases were not related to HBV reactivation.

Related news was previously issued by UK MHRA, and was reported in the Drug News Issue No. 94. DH issued a letter to inform local healthcare professionals to draw their attention on the risk of HBV reactivation of the drug on 16 August 2017. In December 2017, the Registration Committee discussed the matter and noted that Johnson HK had submitted application to update the package insert of the drug. This application has being reviewed and the updated package insert will include the safety information on the risk of HBV reactivation. DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Drug Recall

DH endorsed recall of tablet for relief of allergic symptoms

On 1 December 2017, DH endorsed a licensed drug wholesaler, Kai Yuen Pharmaceutical Company (Kai Yuen), to recall a batch (Lot No./ Mfg. Lot No.: C18) of Finska Tablet 10mg (HK-57988) from the market due to quality issue.

During DH's market surveillance, samples of the above product were collected for analysis and examination. Upon testing by the Public Health Laboratory Services Branch of the Centre for Health Protection, samples of the product were found to have exceeded the pharmacopoeial requirements on bacterial counts. Kai Yuen

Drug Recall

voluntarily recalls the above batch from the market.

Finska Tablet 10mg contains loratadine, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap 138) and is used for the relief of allergic symptoms. According to the wholesaler, the affected batch has been supplied to private doctors, local pharmacies and other wholesaler.

As on 5 January 2018, DH has not received any ADR case in connection with the product. A notice was posted on the Drug Office website on 1 December 2017 to alert the public of the product recall.

DH endorsed batch recall of JeceFARMA Rabeprazole Sodium Enteric Coated 20mg tablets (HK-63779)

On 7 December 2017, DH endorsed a licensed drug wholesaler, Julius Chen & Co (HK) Ltd (Julius Chen), to recall a batch (batch number: DJP 1501) of JeceFARMA Rabeprazole Sodium Enteric Coated 20mg tablets (HK-63779) from the market due to a quality issue.

During DH's market surveillance, samples of the above product were collected for analysis. Testing results from the Government Laboratory revealed that the active ingredient content of the samples was found to be less than the labelled claim, which might affect the efficacy of the product.

Julius Chen has voluntarily recalled the product from the market and was instructed to report the root cause upon investigation by the manufacturer.

The above pharmaceutical product, containing rabeprazole, is a prescription-only medicine used to suppress gastric acid production. According to the wholesaler, the product has been supplied to local private doctors and other wholesalers.

As on 5 January 2018, DH has not received any ADR case in connection with the above product. A notice was posted on the Drug Office website on 7 December 2017 to alert the public of the product recall.

Drug Incident

Public urged not to buy or consume virility product with undeclared and controlled ingredients vardenafil and pseudovardenafil

On 29 December 2017, DH urged the public not to buy or consume a virility product called W+ Boom Boom as it had been found to contain undeclared Part 1 poisons.

Acting on intelligence, DH purchased a sample of the above product for analysis. Results from the Government Laboratory confirmed that the sample contained the Part 1 poisons, vardenafil and pseudovardenafil. DH initiated a joint operation with the Police on 29 December 2017 and raided a company selling the product in Kwai Chung. A woman aged 73 was arrested by the Police for suspected illegal sale and possession of Part 1 poisons.

Vardenafil is a virility drug which should only be used under the advice of a doctor. Side effects of vardenafil include low blood pressure, headache, vomiting, dizziness and transient vision disturbances. It may interact with some drugs (such as nitroglycerin for the treatment of angina) and cause a decrease in blood pressure to dangerous levels. Improper use of vardenafil may pose serious health risks, especially for patients with heart problems. Pseudovardenafil, being chemically similar to vardenafil, is expected to pose similar health risks.

The public may visit the Drug Office's page for a health message on sexual dysfunction and virility products and information on virility products found to contain undeclared Western medicines.

A notice was posted on the Drug Office website on 29 December 2017 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.

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: ***Pharmacovigilance Unit,***
Drug Office, Department of Health,
Rm 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wan Chai, Hong Kong

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.