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 April 2019 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

Singapore: Esmya (ulipristal acetate) and risk of serious liver injury

On 2 April 2019, the Singapore Health Sciences Authority (HSA) announced that Zuellig Pharma Pte Ltd would like to update healthcare professionals on the risk of serious liver injury associated with the use of Esmya (ulipristal acetate). Cases of serious liver injury had been reported overseas in patients treated with Esmya. The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded from its review that Esmya may have contributed to the development of some cases of serious liver injury.

To minimise the risk of serious liver injury associated with the use of Esmya, Zuellig Pharma will be updating the Singapore package insert of Esmya to include warnings on this risk and to inform of the need for liver function monitoring before, during and after treatment with Esmya. The indications for use will also be revised to highlight that Esmya should only be used for the intermittent treatment of moderate to severe symptoms of uterine fibroids, in women of reproductive age who are not eligible for surgical treatment. Esmya continues to be indicated for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age.

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 of 6 May 2019, the Department of Health (DH) has not received any case of adverse drug reaction (ADR) related to Esmya. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 98, 100, 103 and 106. 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. On 12 December 2018, the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the matter and decided that the relevant warnings should be included in the package insert of the product. The DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

Singapore: Actemra® (tocilizumab) and risk of hepatotoxicity

On 11 April 2019, the HSA announced that F. Hoffmann-La Roche would like to inform healthcare professionals on the risk of hepatotoxicity associated with the use of Actemra® (tocilizumab). Serious drug-induced liver injuries, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplant, have been observed with the administration of Actemra®. The frequency of serious hepatotoxicity is considered rare.

The current approved Singapore prescribing information does not recommend treatment with Actemra® in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 5X upper limit of normal (ULN). Caution should be exercised when considering initiation of Acetmra® treatment in patients with ALT or AST above 1.5X ULN.

It is now recommended for patients with Rheumatic

Arthritis, Polyarticular Juvenile Idiopathic Arthritis and Systemic Juvenile Idiopathic Arthritis, to be monitored for their ALT and AST every 4 to 8 weeks for the first 6 months of treatment followed by every 12 week thereafter. Recommended dose modifications (reduction, interruption or discontinuation) of Actemra® due to liver enzyme abnormalities remain unchanged in drug label.

In Hong Kong, there are 4 registered pharmaceutical products containing tocilizumab, namely Actemra Conc for Soln for Infusion 400mg/20ml (HK-59200), Actemra Conc for Solution for Inf 200mg/10ml (HK-59201), Actemra Conc for Soln for Infusion 80mg/4ml (HK-59202) and Actemra Solution for Injection in Pre-filled Syringe 162mg/0.9ml (HK-63771). All products are registered by Roche Hong Kong Limited, and are prescription-only medicines. As of 6 May 2019, the DH has received 8 cases of ADR related to tocilizumab, but these cases are not related to hepatotoxicity. In light of the above HSA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 12 April 2019. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

EU: Use of multiple sclerosis medicine Lemtrada restricted while EMA review is ongoing

On 12 April 2019, the EMA of the European Union (EU) announced that it has started a review of the multiple sclerosis medicine Lemtrada (alemtuzumab) following new reports of immune-mediated conditions (caused by the body's defence system not working properly) and problems with the heart and blood vessels with the medicine, including fatal cases.

As a temporary measure while the review is ongoing, Lemtrada should only be started in adults with relapsing-remitting multiple sclerosis that is highly active despite treatment with at least two disease-modifying therapies (a type of multiple sclerosis medicine) or where other disease-modifying therapies cannot be used. Patients being treated with Lemtrada who are benefitting from it may continue treatment in consultation with their doctor.

In addition to the restriction, the EMA's safety committee (PRAC) has recommended an update of the product information for Lemtrada to inform patients and healthcare professionals about cases of:

- immune-mediated conditions, including autoimmune hepatitis (with damage to the liver) and haemophagocytic lymphohistiocytosis (overactivation of the immune system which may affect different parts of the body);
- problems with the heart and blood vessels occurring within 1–3 days of receiving the medicine, including bleeding in the lungs, heart attack, stroke, cervicocephalic arterial dissection (tears in the lining of the arteries in the head and neck);
- severe neutropenia (low levels of neutrophils, a type of white blood cell that fights infections).

Healthcare professionals should consider stopping treatment in patients who develop signs of these conditions and patients should immediately seek medical help if they experience symptoms.

Information for healthcare professionals

- Doctors are being informed in writing of temporary restrictions on the prescription of Lemtrada pending the conclusion of an ongoing review of the medicine and inclusion of new safety warnings in the product information of Lemtrada.
- New treatment should only be initiated in adults with relapsing-remitting multiple sclerosis that is highly active despite a full and adequate course of treatment with at least two other disease-modifying therapies, or in adults with highly active relapsing-remitting multiple sclerosis where all other disease-modifying therapies are contraindicated or otherwise unsuitable.
- For patients being treated with Lemtrada, vital signs should be monitored before and during the intravenous infusion. If clinically significant changes are observed, discontinuation of infusion and additional monitoring, including ECG, should be considered.
- Liver function tests should be carried out before and during treatment. If patients

develop signs of liver damage, unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g. unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice or dark urine), Lemtrada should only be re-administered following careful consideration.
- Patients who develop signs of pathological immune activation should be evaluated immediately, and a diagnosis of haemophagocytic lymphohistiocytosis considered. Symptoms of immune activation may occur up to 4 years after the start of treatment.
- Further information will be provided once the review of Lemtrada is concluded.

In Hong Kong, Lemtrada Concentrate for Solution for Infusion 12mg/1.2ml (HK-64543) is a registered pharmaceutical product containing alemtuzumab. The product is registered by Sanofi-Aventis Hong Kong Limited, and is a prescription-only medicine. As of 6 May 2019, the DH has received one case of ADR for alemtuzumab related to immune functions.

Related news on warning about rare but serious risks of stroke and blood vessel wall tears associated with Lemtrada (alemtuzumab) was released by the United States (US) Food and Drug Administration (FDA) and was reported in the Drug News Issue No. 109. The DH issued a letter to inform local healthcare professionals to draw their attention on the warnings on 30 November 2018; and the matter will be discussed by the Registration Committee.

In light of the above EMA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 15 April 2019. Since EMA's review is on-going, the DH will remain vigilant on the conclusion of the EMA review and any safety updates on alemtuzumab issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

UK: Elvitegravir boosted with cobicistat: avoid use in pregnancy due to risk of treatment failure and maternal-to-child transmission of HIV-1

On 16 April 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that pharmacokinetic data indicate exposure of elvitegravir boosted with cobicistat (Genvoya▼, Stribild) is lower during the second and third trimesters of pregnancy than postpartum. Low elvitegravir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child, and therefore elvitegravir/cobicistat should not be used during pregnancy.

Elvitegravir is an integrase inhibitor that is used as one of the concomitant antiretroviral therapies to treat HIV-1. Cobicistat is a pharmacokinetic enhancer used to increase elvitegravir levels.

In July 2018, the MHRA issued warnings not to use darunavir boosted with cobicistat in pregnancy after pharmacokinetic data suggested an increased risk of treatment failure and mother-to-child transmission of HIV infection due to lower exposures during pregnancy. The risk in treatments containing elvitegravir/cobicistat has also been reviewed.

Pharmacokinetic data from IMPAACT P1026s (International Maternal Pediatric Adolescent AIDS Clinical Trials P1026 study) show that compared with paired postpartum data, plasma concentration after 24 hours of elvitegravir boosted with cobicistat was 81% lower in the second trimester and 89% lower in the third trimester. Plasma concentration after 24 hours of cobicistat was 60% and 76% lower in the second and third trimester, respectively.

A review of safety data and the published literature has not identified any cases of mother to child HIV-1 transmission in women taking regimens containing elvitegravir/cobicistat during the second and third trimesters of pregnancy. However, due to the theoretical risk, therapy with elvitegravir/cobicistat should not be initiated during pregnancy and women who are pregnant and taking elvitegravir/cobicistat should be switched to an alternative regimen.

The product information for Genvoya▼ (elvitegravir/cobicistat/emtricitabine/tenofovir

alafenamide) and Stribild (elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil) are being updated to recommend against use in pregnancy in the UK.

Healthcare professionals are advised:

- Pharmacokinetic data show low exposure values of elvitegravir boosted with cobicistat (elvitegravir/cobicistat) during the second and third trimesters of pregnancy.
- Although no cases have been reported of such transmission on elvitegravir/cobicistat therapy as of 16 April 2019, low elvitegravir exposure may be associated with an increased risk of treatment failure and an increased risk of mother-to-child transmission of HIV infection.
- Therapy with elvitegravir/cobicistat should not be initiated during pregnancy.
- Switch women who are pregnant and taking elvitegravir/cobicistat to an alternative regimen.

In Hong Kong, Stribild Tablets (HK-62550), Stribild Tablets (HK-64384) and Genvoya Tablets (HK-64455) are registered pharmaceutical products containing elvitegravir/cobicistat. These products are registered by Gilead Sciences Hong Kong Limited, and are prescription-only medicines. As of 6 May 2019, the DH has received one case of ADR related to Genvoya, but this case is not related to treatment failure in pregnancy or maternal-to-child transmission of HIV-1. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 17 April 2019 and the matter will be discussed by the Registration Committee.

UK: Yellow fever vaccine (Stamaril) and fatal adverse reactions: extreme caution needed in people who may be immunosuppressed and those 60 years and older

On 16 April 2019, the MHRA announced that it has recently received 2 reports of fatal adverse reactions to the yellow fever vaccine (Stamaril). Due to an increased risk of life-threatening reactions, the vaccine must not be given to anyone with a medical history of thymus dysfunction or who is immunosuppressed. In addition, extreme caution must be used and a careful risk assessment conducted before vaccination of people aged 60 years and older due to a substantially increased risk of such adverse reactions in this age group.

In recent months, the MHRA has been notified of 2 fatal adverse reactions to yellow fever vaccine. In one case, the vaccine was given to a person with a history of thymectomy following a thymoma (a contraindication in the product information). In another case, the vaccine was given to a 67-year-old with no other known risk factors. Both patients died shortly after vaccination due to suspected yellow fever vaccine-associated viscerotropic disease (YEL-AVD). YEL-AVD is a recognised adverse reaction that resembles severe yellow fever infection. The global reporting rate is around 1 case in every 1 million people vaccinated, with thymus disease, immunosuppression, and an age of 60 years and older increasing the risk. Another serious risk of vaccination is vaccine-associated neurotropic disease (YEL-AND), which can occur at a similar rate and with the same risk factors. YEL-AND can present with a variety of neurological manifestations.

The MHRA is in the process of reviewing the benefit-risk balance of yellow fever vaccine and measures to minimise risks in the light of these cases and the latest scientific data. The MHRA will update guidance, as necessary.

When a person presents for yellow fever immunisation, it is important that healthcare professionals clearly discuss with them the individual risks and benefits of the vaccine based on their specific travel itinerary. Sufficient time should be set aside to ensure that the person is immune competent and has no contraindications to the vaccine, including a review of full medical history and any available medical records. Any potential history of thymus disease or thymus removal should be specifically queried. Any decision to administer the vaccine to a person aged 60 years and older must be based on a significant and unavoidable risk of acquiring yellow fever infection. Provision of the Patient Information Leaflet would provide a helpful basis for this discussion with potential vaccinees. Risk assessment checklists should also be used to ensure checks have been completed and patients have been

assessed for immunocompetence (in line with local and organisational requirements).

Healthcare professionals are reminded:

- As with any live attenuated vaccine, yellow fever vaccine must not be given to people who may be immunosuppressed.
- Yellow fever vaccine is contraindicated in people with a history of thymus dysfunction (including myasthenia gravis and thymoma).
- Yellow fever vaccine is contraindicated in people who have had their thymus gland removed (thymectomy).
- In people aged 60 years and older, the vaccine should only be given when it is considered that there is a significant and unavoidable risk of acquiring yellow fever infection.
- Professionals who administer yellow fever vaccine must be familiar with any contraindications and special precautions before proceeding with immunization.
- If there is any doubt as to whether a person who is due to receive yellow fever vaccine may be immunosuppressed, immunisation should be deferred until specialist advice has been sought.
- Protocols and checklists should be strengthened to avoid inappropriate administration that can lead to severe and possibly fatal adverse effects.

In Hong Kong, Stamaril Pasteur (Yellow Fever) Vaccine (HK-40600) is registered by Sanofi-Aventis Hong Kong Limited, and is a prescription-only medicine. As of 6 May 2019, the DH has received one case of adverse event following Stamaril vaccination. The case was reported to the DH as a case of yellow fever vaccine-associated viscerotropic disease (YEL-AVD). The case had a few clinical features compatible with YEL-AVD. However, according to the opinion of the World Health Organization (WHO) Yellow Fever Initiative, it cannot be concluded that this case was a definite case of YEL-AVD.

The local product insert states that the drug should not be used in patients who have a poor or weakened immune system or have a history of problems with their thymus gland or have had their thymus gland removed. The product insert also includes warnings and precautions for patients who are over 60 years old. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

EU: EMA recommends withdrawal of marketing authorisation for cancer medicine Lartruvo

On 26 April 2019, the EMA announced that it has completed its assessment of the results of the ANNOUNCE study and concluded that Lartruvo (olaratumab) with doxorubicin does not prolong the lives of patients with soft tissue cancer more than doxorubicin alone. The EMA is therefore recommending that the marketing authorisation of the medicine be revoked.

In January 2019, when preliminary results of the ANNOUNCE study became available, the EMA recommended that no new patients should start treatment with the medicine. Having now assessed the full data from the study, the EMA has concluded that the benefit of Lartruvo in combination with doxorubicin is not confirmed. Regarding safety, the data did not show any new safety concerns.

Lartruvo was authorised by the EMA in November 2016 to treat advanced soft tissue sarcoma, a condition for which there is paucity of suitable medicines. At the time of its approval, data on the effects of Lartruvo were limited because of the small number of patients included in the main study which supported its authorisation. The medicine was therefore granted a conditional marketing authorisation on condition that the company provided additional data from the ANNOUNCE study.

The Committee for Medicinal Products for Human Use (CHMP) opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

Information for patients

- Lartruvo was approved to treat a rare type of cancer called soft tissue sarcoma. It was approved on condition that the company carried out a study to confirm its benefits.

- However, that study showed that Lartruvo with doxorubicin is no better than doxorubicin alone at prolonging patients' lives.
- The marketing authorisation of Lartruvo will therefore be withdrawn and no new patients will be treated with the medicine.
- If they are already being treated with Lartruvo, their doctor will consider the most appropriate treatment for them.
- There are no new safety concerns with the medicine.

Information for healthcare professionals

- The phase 3 study ANNOUNCE of Lartruvo in combination with doxorubicin in patients with advanced or metastatic soft tissue sarcoma did not confirm the clinical benefit of Lartruvo.
- The study did not meet its primary objective to prolong survival in the overall population (stratified hazard ratio [HR]: 1.05; median 20.4 for Lartruvo plus doxorubicin versus 19.8 months for placebo plus doxorubicin) or in the leiomyosarcoma sub-population (HR: 0.95; median 21.6 months for Lartruvo plus doxorubicin versus 21.9 months for placebo plus doxorubicin).
- Additionally, no benefit was shown in terms of prolonging progression-free survival in the overall population (HR: 1.23; median 5.4 months for Lartruvo plus doxorubicin versus 6.8 months for placebo plus doxorubicin), which was one of the secondary objectives of the study.
- As a consequence, the marketing authorisation of Lartruvo will be revoked and no new patients will be able to receive Lartruvo.
- For patients already on treatment with Lartruvo, doctors should consider the available treatment options.
- No new safety concerns were identified during the study.

In Hong Kong, there are 2 registered pharmaceutical products containing olaratumab, namely Lartruvo Concentrate for Solution for Infusion 500mg/50ml (HK-66024) and Lartruvo Concentrate for Solution for Infusion 190mg/19ml (HK-66025). Both products are registered by Eli Lilly Asia, Inc. (Eli Lilly), and are prescription-only medicines. As of 6 May 2019, the DH has not received any case of ADR related to olaratumab. Related news was previously issued by the EMA and Health Canada, and was reported in the Drug News Issue No. 111. The DH issued a letter to inform local healthcare professionals to draw their attention on 24 January 2019.

In light of the above EMA's recommendation, the DH will follow up with Eli Lilly, and the matter will be discussed by the Registration Committee.

US: Teva Pharmaceuticals USA, Inc. issues voluntary nationwide recall of Losartan Potassium 25 mg and 100 mg Tablets USP, sold exclusively to Golden State Medical Supply

On 26 April 2019, the US FDA announced that Teva Pharmaceuticals USA, Inc. has initiated a voluntary recall in the US, to the patient level, of 35 lots of bulk Losartan Potassium USP Tablets (6 lots of 25 mg strength and 29 lots of 100 mg strength). This recall is due to the detection of an impurity – *N*-nitroso-*N*-methyl-4-aminobutyric acid (NMBA) – found in six lots of active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited that is above the US FDA's interim acceptable exposure limit of 9.82 ppm. Based on the available information, the risk of developing cancer in a few patients following long-term use of the product cannot be ruled out. The lots were sold exclusively to Golden State Medical Supply (GSMS) of Camarillo, California. GSMS packages this bulk product under its own label and distributes in retail bottles of 30, 90, and 1000 tablets.

The finished product lots that are included in this voluntary recall and listed below were sold by Teva in bulk containers. The tablets were repackaged for further distribution by GSMS under its product label. The bulk tablet lots were repackaged into 44 finished products lots for further distribution by GSMS under its product label.

GSMS Finished Goods (FG) National Drug Codes (NDCs)	GSMS FG NDC Description	GSMS FG Product Lot Numbers	Expiration Dates
60429-316 -30	Losartan Potassium, Tablets, USP, 25 mg, 30 Count Bottle	GS017981, GS016958, GS017341	02/2020
60429-316 -90	Losartan Potassium, Tablets, USP, 25 mg, 90 Count Bottle	GS015172	06/2019
		GS017634, GS017653, GS017980, GS016726, GS017045, GS017276	02/2020
60429-316 -10	Losartan Potassium, Tablets, USP, 25 mg, 1,000 Count Bottle	GS014817, GS015204	06/2019
		GS018318, GS017342, GS017808	02/2020
60429-318 -90	Losartan Potassium, Tablets, USP, 100 mg, 90 Count Bottle	GS014045, GS014305, GS014044	06/2019
		GS016535, GS016524, GS017385, GS017539, GS017540, GS017543, GS017542	01/2020
		GS017384, GS017984, GS017985, GS017986, GS018263, GS018264, GS018265	02/2020
60429-318 -10	Losartan Potassium, Tablets, USP, 100 mg, 1,000 Count Bottle	GS014054	06/2019
		GS016338	12/2019
		GS016341, GS016342, GS016343, GS016344, GS016345, GS016539, GS016969, GS016973, GS017337	1/2020
		GS018524	02/2020

The affected Losartan Potassium tablets being recalled are described as:

- Losartan Potassium tablets, USP 25 mg, are light-green, film-coated, teardrop-shaped biconvex tablet with “LK 25” on one side and ">" on the other side.
- Losartan Potassium tablets, USP 100 mg, are dark green, film-coated, oval-shaped biconvex tablets with “LK100” on one side and ">" on the other side.

As of 26 April 2019, Teva has not received any reports of adverse events related to the lots being recalled.

No other Teva Losartan Potassium finished drug products have been identified, in the US, containing API above the interim specification levels set for NMBA.

Teva promptly notified GSMS of the presence of the impurity in Hetero’s API and Teva will recall 35 lots of bulk Losartan Potassium tablets sold to that company. The tablets, which have been packaged and sold by GSMS, will be recalled from their customers and patients. Distributors and retailers that have product being recalled should immediately stop distribution, quarantine all remaining product in their control, and return the recalled product per the instructions given to them by GSMS.

In Hong Kong, the above products are not registered pharmaceutical products.

In Hong Kong, as of 6 May 2019, there are 245 registered pharmaceutical products containing valsartan (83 products), candesartan (19 products), irbesartan (62 products), losartan (64 products) and olmesartan (17 products). All products are prescription-only medicines.

Regarding impurities in sartan-containing products, a public announcement was first issued on 6 July 2018, and the DH issued letters to inform local healthcare professionals on 6 July 2018, 9 July 2018, 25 July 2018 and 3 August 2018. Related news was also previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 105, 106, 107, 108, 109, 110, 111, 112 and 113.

Regarding the announcements issued by various overseas drug regulatory authorities on the detection of *N*-nitrosodimethylamine (NDMA) and

N-nitrosodiethylamine (NDEA) in sartan-containing products, the following 5 valsartan products and 1 irbesartan product were affected and recalled from the Hong Kong market on 6 July 2018 and 20 December 2018 respectively: HK-61786, HK-61787, HK-61784, HK-61785, HK-60794 and HK-63378. The recalls were reported in the Drug News Issue No. 105 and 110. The DH noted that these recalls were completed.

The DH had collected samples of sartan-containing products in the local market for analysis. No NDMA and NDEA were detected.

Regarding the announcements issued by various overseas drug regulatory authorities on the detection of NMBA in losartan, the DH endorsed the recall of 4 losartan products (HK-61932, HK-61933, HK-62634 and HK-62635) from the local market as a precautionary measure due to the potential for NMBA in the products on 11 March 2019. The recall was reported in the Drug News Issue No. 113. The DH noted that the recall was completed.

As of 6 May 2019, the DH has received 17 cases of ADR related to valsartan, candesartan, irbesartan, losartan and olmesartan. None of them is concluded to be related to the presence of impurities such as NDMA, NDEA and/or NMBA. The DH has provided update information at Drug Office's website (www.drugoffice.gov.hk) and will keep vigilant on any safety updates on detection of impurities in sartan-containing products issued by overseas regulatory authorities.

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

US: FDA adds Boxed Warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines

On 30 April 2019, the US FDA advised that rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have also resulted in deaths. These behaviors appear to be more common with eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) than other prescription medicines used for sleep.

As a result, the FDA is requiring a Boxed Warning, its most prominent warning, to be added to the prescribing information and the patient medication guides for these medicines. The FDA is also requiring a Contraindication, its strongest warning, to avoid use in patients who have previously experienced an episode of complex sleep behavior with eszopiclone, zaleplon, and zolpidem.

Serious injuries and death from complex sleep behaviors have occurred in patients with and without a history of such behaviors, even at the lowest recommended doses, and the behaviors can occur after just one dose. These behaviors can occur after taking these medicines with or without alcohol or other central nervous system depressants that may be sedating such as tranquilizers, opioids, and anti-anxiety medicines.

Healthcare professionals should not prescribe eszopiclone, zaleplon, or zolpidem to patients who have previously experienced complex sleep behaviors after taking any of these medicines. Advise all patients that although rare, the behaviors caused by these medicines have led to serious injuries or death. Tell the patient to discontinue taking these medicines if they experience an episode of complex sleep behavior.

Patients should stop taking their insomnia medicine and contact their healthcare professional right away if they experience a complex sleep behavior where they engage in activities while they are not fully awake or if they do not remember activities they have done while taking the medicine.

The FDA identified 66 cases of complex sleep behaviors occurring with these medicines over the past 26 years that resulted in serious injuries, including death. This number includes only reports submitted to the FDA or those found in the medical literature, so there may be additional cases about which the FDA is unaware. These cases included accidental overdoses, falls, burns, near drowning, exposure to extreme cold temperatures leading to

loss of limb, carbon monoxide poisoning, drowning, hypothermia, motor vehicle collisions with the patient driving, and self-injuries such as gunshot wounds and apparent suicide attempts. Patients usually did not remember these events. The underlying mechanisms by which these insomnia medicines cause complex sleep behaviors are not completely understood.

In Hong Kong, there are 18 registered pharmaceutical products containing zolpidem, and all products are prescription-only medicines. There is no registered pharmaceutical product containing eszopiclone or zaleplon. As of 6 May 2019, the DH has received 3 cases of ADR related to zolpidem, but these cases are not related to sleepwalking. The DH has not received any case of ADR related to eszopiclone or zaleplon.

News related to the safety of zolpidem, including risk of complex sleep behaviours, was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 1, 26, 39, 43 and 53. The DH issued letters to inform local healthcare professionals to draw their attention on 6 December 2011 and 11 January 2013. In light of the above FDA's announcement on the new contraindication, the DH issued a letter to inform local healthcare professionals to draw their attention on 2 May 2019, and the matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed batch recall of Syntometrine Injection (HK-01698)

On 3 April 2019, the DH endorsed a licensed drug wholesaler, Healthcare Division O/B DCH Auriga (Hong Kong) Limited (Auriga), to recall one batch (batch number: 60748) of Syntometrine Injection (HK-01698) from the market because of a potential quality issue.

The DH received notification from Auriga that the manufacturer of the product in Germany reported that, during handling a complaint of content discoloration, the results revealed the content of the active ingredients and degradation products of the batch were out of specification, which might affect the efficacy of the product. According to the preliminary investigation by the manufacturer, other batches are not affected by the issue.

Auriga voluntarily recalled the batch of the product from the market and was instructed to report the root cause to the DH upon investigation by the manufacturer in Germany.

The above product, containing Ergometrine and Oxytocin, is a prescription medicine used for active management of the third stage of labour and treatment of post-partum haemorrhage. According to Auriga, the affected batch of product has been supplied to the Hospital Authority, private hospitals and a private doctor.

As of 6 May 2019, the DH has not received any case of ADR in connection with the affected batch of the product. Press release was posted on the Drug Office website on 3 April 2019 to alert the public of the product recall.

DH endorsed batch recall of Revonto (Dantrolene sodium for injection)

On 25 April 2019, the DH endorsed a licensed drug wholesaler, Sino-Asia Pharmaceutical Supplies Ltd. (Sino-Asia), to recall one batch of Revonto (Dantrolene sodium for injection) (batch number: 17REV01A) from the market because of a potential quality issue.

The DH received notification from Sino-Asia that the distributor of the above product in the US had informed Sino-Asia to recall one batch (17REV01A) of the product from the market because the reconstituted solution of the batch was found to be non-clear during the routine stability study.

The above product, containing dantrolene sodium, is used for the management of malignant hyperthermia crisis. It is not a registered pharmaceutical product in Hong Kong but was imported for the treatment of particular patients by

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registered medical practitioners. According to Sino-Asia, 5 packs (each pack contains 6 vials) of the affected batch have been imported and supplied to the Hospital Authority. A notice was posted on the Drug Office website on 25 April 2019 to alert the public of the product recall.

Drug Incident

Public urged not to buy or consume slimming products with undeclared controlled ingredient sibutramine

On 4 April 2019, the DH appealed to the public not to buy or consume two slimming products named Leg Step and Bello Smaze as they were found to contain an undeclared and controlled drug ingredient that might be dangerous to health.

Following a public complaint, samples of the above slimming products were purchased via a social media platform for analysis. Test results from the Government Laboratory revealed that the samples of both products contain sibutramine, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138).

Sibutramine was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of increased cardiovascular risk.

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.

The public may visit the Drug Office's pages for health messages on weight control and slimming products and information on slimming products with undeclared Western drug ingredients .

Press release was posted on the Drug Office website on 4 April 2019 to alert the public of the drug incident.

DH urged public not to buy or consume virility product with undeclared controlled ingredients lignocaine and sildenafil

On 16 April 2019, the DH urged the public not to buy or consume a virility product called Blue M as it was found to contain undeclared controlled ingredients.

Acting on a public complaint, samples of the above product, with each pack containing two capsules and one wet wipe, were collected for analysis by the Government Laboratory. The test results confirmed that samples of the wet wipe contained lignocaine, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138), while one sample of the capsules also contained another Part 1 poison, sildenafil.

Based on the laboratory results, the DH and the Police raided a retailer in Mong Kok in a joint operation on 16 April 2019 during which a woman aged 26 was arrested for suspected illegal sale and possession of Part 1 poisons and unregistered pharmaceutical product.

Sildenafil is a prescription drug used for erectile dysfunction and should be taken under a doctor's advice and supplied at pharmacies under the supervision of a registered pharmacist upon a doctor's prescription. Side effects of sildenafil 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 sildenafil may pose serious health risks, especially for patients with heart problems. Lignocaine is a local anaesthetic and may cause hypersensitivity reactions.

The public may visit the Drug Office's webpage for health messages on sexual dysfunction and virility products and the list of virility products found to contain undeclared western medicines for more information.

Press release was posted on the Drug Office website on 16 April 2019 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 accordnance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

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.