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 August 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

UK: Ibrutinib (Imbruvica ▼): reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and of opportunistic infections

On 15 August 2017, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that a routine European review examined the safety profile of ibrutinib. Data from randomised controlled trials and the scientific literature were assessed. Worldwide spontaneous suspected adverse drug reaction (ADR) reports were also reviewed from a cumulative post-marketing exposure of approximately 38,000 patient-years.

Regarding ventricular tachyarrhythmia, randomised controlled trials reported a slightly increased risk of ventricular tachyarrhythmia with ibrutinib. In a 2017 study of case reports of relevant events from post-marketing sources and clinical trial data, the authors identified 11 cases of ventricular tachycardia/ventricular fibrillation and 6 cases of sudden cardiac death in patients exposed to ibrutinib. In 12 of these 17 cases, the events occurred without any evidence of prior cardiac history. The review also identified 2 spontaneous ADRs of ventricular tachyarrhythmia in which the role of ibrutinib could not be excluded. The product information of ibrutinib in UK is being updated to include ventricular tachyarrhythmia as a common adverse reaction (thought to occur in fewer than 10 in 100 patients taking ibrutinib post-marketing).

Regarding hepatitis B virus reactivation, data were not available from clinical trials since all patients had been pre-screened for hepatitis B status and those who tested positive were excluded from studies. The review identified 8 cases of hepatitis B reactivation in which the role of ibrutinib was considered probable or possible. The product information of ibrutinib in UK is being updated to include hepatitis B virus reactivation as an uncommon adverse reaction.

Regarding opportunistic infections, infections are a frequent co-morbidity in patients with the haematological malignancies in which ibrutinib is indicated. The review identified 157 cases of aspergillosis among patients exposed to ibrutinib in post-marketing settings, 43 of which were fatal. The review also identified 44 cases of Pneumocystis Jirovecii pneumonia (PJP), none of which were fatal. In clinical trials, ibrutinib did not appear to raise the risk of aspergillosis or PJP compared with comparator treatments. The product information for ibrutinib in UK already lists opportunistic infections as very common adverse reactions (thought to affect more than 10 in 100 patients taking the drug post-marketing).

Healthcare professionals are advised:

- cases of ventricular tachyarrhythmia have been reported;
- temporarily discontinue ibrutinib in patients who develop symptoms suggestive of ventricular arrhythmia, including palpitations, chest pain, dyspnoea, dizziness, or fainting, and assess benefit-risk before restarting therapy;
- be aware of the risk of hepatitis B virus reactivation and establish hepatitis B virus status before initiating therapy;
- for patients with positive hepatitis B serology, consultation with a liver disease expert is

recommended before the start of treatment; monitor and manage patients according to local medical standards of care to minimise the risk of hepatitis B virus reactivation; and
- consider prophylaxis according to standard of care for patients who are at an increased risk of opportunistic infections.

In Hong Kong, there is one pharmaceutical product containing ibrutinib, namely Imbruvica Capsules 140mg (HK-64088) which is registered by Johnson & Johnson (Hong Kong) Ltd., and is a prescription-only medicine. As on 25 September 2017, the Department of Health (DH) has received 7 cases of ADR related to ibrutinib, but these cases were not related to ventricular tachyarrhythmia, hepatitis B reactivation or opportunistic infections. DH issued a letter to inform local healthcare professionals to draw their attention on the above safety information on 16 August 2017. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (Registration Committee).

UK: Corticosteroids: rare risk of central serous chorioretinopathy with local as well as systemic administration

On 15 August 2017, MHRA announced that central serous chorioretinopathy (CSCR), a retinal disorder, has been linked to the systemic use of corticosteroids. Recently, it has also been reported after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes.

CSCR is characterised by the accumulation of subretinal fluid at the posterior pole of the fundus, ultimately causing retinal detachment. CSCR typically affects one eye only and can cause vision to be blurry and distorted, with objects often appearing smaller and distorted in the affected eye. Patients may also have difficulty with bright lights and contrast sensitivity. Although the exact mechanism that leads someone to develop CSCR is unknown, several possible risk factors have been described, including use of systemic corticosteroids, pregnancy, and Cushing's syndrome. These risks are thought to be associated with the effect of cortisol on the eye.

CSCR has recently also been described after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes. It is a rare side effect that occurs with all formulations. Although blurred vision is a symptom of CSCR, it is also an established side effect of steroid treatment. The causes of blurred vision are various and can also include cataract and glaucoma.

Healthcare professionals are advised on the followings:
- advise patients to report any blurred vision or other visual disturbances during corticosteroid treatment; and
- consider referral to an ophthalmologist for evaluation of possible causes if a patient presents with vision problems.

In Hong Kong, depending on the types and presentations of the corticosteroids, preparations containing corticosteroids can be prescription-only medicines or pharmacy-only medicines. As on 25 September 2017, DH has not received any case of ADR related to central serous chorioretinopathy. DH issued a letter to inform local healthcare professionals to draw their attention on the safety information on 16 August 2017. The matter will be discussed by the Registration Committee.

EU: Tick and flea control agent Bravecto continues to be acceptably safe to use. New adverse reaction to be included in package leaflet.

On 17 August 2017, the European Medicines Agency (EMA) of European Union (EU) announced that EMA concluded in July 2017 that Bravecto, a medicine that treats tick and flea infestations in dogs and cats, continues to have an acceptable safety profile. However, the company that markets the product will have to update the package leaflet and include convulsions as a new side effect that is reported very rarely, i.e., less than one animal out of 10,000 animals treated. Veterinarians and pet owners will also be advised to use Bravecto with caution in dogs with epilepsy.

EMA's Committee for Medicinal Products for Veterinary Use (CVMP), following a regular but inconclusive analysis of limited data on serious side effects, had requested the company to investigate all relevant reports related to various disorders such as neurological, skin and appendage

diseases, hypersensitivity or immune-mediated reactions and liver diseases, some of which were fatal. The investigation had to take into account the age and breed of animals, the number of treatments, underlying disease conditions and concomitant treatments. According to the company, about 41.6 million doses had been distributed worldwide, of which approximately 18 million were in EU between February 2014 and December 2016. By 15 August 2017, suspected side effects had been reported electronically for 5,326 dogs, of which 2,144 were in EU. Between February 2014 and 15 August 2017, deaths had been reported in 1,265 dogs worldwide and 342 in EU. Each report relates to dogs under different health conditions, often receiving multiple medicines, therefore these figures may or may not be related to the use of Bravecto in dogs.

In Hong Kong, there are 5 Bravecto (fluralaner) products, including Bravecto Chewable Tablets For Very Small Dogs 112.5mg (Vet) (HK-65276), Bravecto Chewable Tablets For Small Dogs 250mg (Vet) (HK-65277), Bravecto Chewable Tablets For Very Large Dogs 1400mg (Vet) (HK-65278), Bravecto Chewable Tablets For Large Dogs 1000mg (Vet) (HK-65279) and Bravecto Chewable Tablets For Medium-sized Dogs 500mg (Vet) (HK-65280). All products are registered by Merck Sharp & Dohme (Asia) Ltd, and are prescription-only medicines. As on 25 September 2017, DH has not received any case of ADR related to Bravecto (fluralaner). DH issued a letter to inform the Hong Kong Veterinary Association Ltd. of the above safety information on 18 August 2017. The matter will be discussed by the Registration Committee.

US: FDA alerts healthcare professionals and oncology clinical investigators about two clinical trials on hold evaluating KEYTRUDA® (pembrolizumab) in patients with multiple myeloma

On 31 August 2017, the United States (US) Food and Drug Administration (FDA) issued a statement to inform the public, health care professionals, and oncology clinical investigators about the risks associated with the use of KEYTRUDA® (pembrolizumab) in combination with dexamethasone and an immunomodulatory agent (lenalidomide or pomalidomide) for the treatment of patients with multiple myeloma based on data from two recently halted clinical trials. KEYTRUDA® (pembrolizumab) is not approved for treatment of multiple myeloma in US.

The FDA statement is based on review of data from two clinical trials (KEYNOTE-183 and KEYNOTE -185) evaluating the use of KEYTRUDA® (pembrolizumab) combined with other treatments in patients with multiple myeloma. KEYNOTE-183 is a clinical trial with official title 'A Phase III Study of Pomalidomide and Low Dose Dexamethasone With or Without Pembrolizumab (MK3475) in Refractory or Relapsed and Refractory Multiple Myeloma (rrMM)'. KEYNOTE-185 is a clinical trial with official title 'A Phase III Study of Lenalidomide and Low-dose Dexamethasone With or Without Pembrolizumab (MK3475) in Newly Diagnosed and Treatment naïve Multiple Myeloma'. On 3 July 2017, FDA required that all patients in these trials be discontinued from further investigation with this drug, because interim results from both trials demonstrated an increased risk of death for patients receiving KEYTRUDA® (pembrolizumab) when it was combined with an immunomodulatory agent as compared to the control group. Merck & Co., Inc. was made aware of the issue through an external data monitoring committee recommendation and suspended the trials to enrollment on 12 June 2017.

The statement does not apply to patients taking KEYTRUDA® (pembrolizumab) for an approved indication. The safety and efficacy of using KEYTRUDA® (pembrolizumab) for approved, on-label uses have been proven. Patients on KEYTRUDA® (pembrolizumab) for an approved use should continue to take their medication as directed by their health care professional.

KEYTRUDA® (pembrolizumab) is currently approved by FDA for treatment of melanoma, lung cancer, head and neck cancer, classical Hodgkin lymphoma, urothelial carcinoma and microsatellite instability-high (MSI-H) cancer.

Other multiple myeloma clinical trials of KEYTRUDA® (pembrolizumab), other PD-1 (programmed cell death- 1)/PD-L1(programmed cell death 1 ligand 1) cancer drugs and other combinations are currently undergoing clinical evaluation. FDA will be working directly with sponsors of KEYTRUDA® and other PD-1/PD-L1

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cancer drugs, as well as clinical investigators conducting clinical trials in patients with multiple myeloma, to determine the extent of the safety issue. The agency will communicate any new information to the public as soon as it is able.

On 20 September 2017, there is an update posted on US FDA website that FDA has informed multiple investigators who have ongoing clinical trials using PD-1/PD-L1 oncology drugs in combination with immunomodulatory agents or in hematologic malignancies combined with other classes of drugs whether their trials must be temporarily stopped to allow for modifications or must be permanently stopped.

In Hong Kong, Keytruda Solution for Injection 100mg/4ml (HK- 64228) and Keytruda Powder for Injection 50mg (HK- 64229) are pharmaceutical products registered by Merck Sharp & Dohme (Asia) Ltd, and are prescription only medicines. According to the registered packaging inserts, multiple myeloma is not a registered indication of the above products in Hong Kong.

In Hong Kong, a clinical trial certificate is required before conducting a clinical trial of pharmaceutical product. At present, no clinical trial certificates have been approved for conducting clinical trials involving pembrolizumab (Keytruda) and other similar cancer drugs, PD-1 and PD-L1 inhibitors, (as mentioned in US FDA statement) for the treatment of multiple myeloma in Hong Kong. DH will keep vigilant against any safety updates of the drug.

Drug Incident

DH raided retail stall for suspected illegal sale and possession of unregistered pharmaceutical product

On 2 August 2017, DH and the Police conducted a joint operation and raided a retail stall in Tsing Yi for the suspected illegal sale and possession of an unregistered pharmaceutical product named MIAO JIA DU XUAN GAO, which was found to contain undeclared controlled ingredients.

Acting upon a public complaint, a sample of the above product was purchased for analysis. Test results from the Government Laboratory confirmed that the sample contained three Part 1 poisons, namely clobetasol propionate, miconazole and ketoconazole.

A woman aged 44 was arrested for suspected illegal sale and possession of Part 1 poisons and unregistered pharmaceutical products in the operation.

Clobetasol propionate is a steroid substance for treating inflammation. Inappropriate or excessive application of steroids could cause skin problems and body-wide side effects like moon face, high blood pressure, high blood sugar, muscle atrophy, adrenal insufficiency and osteoporosis. Products containing clobetasol propionate should be used under a doctor's directions and be supplied in a pharmacy under supervision of a registered pharmacist upon a doctor's prescription. Miconazole and ketoconazole are used for the treatment of fungal infections with side effects including local irritation and sensitivity reactions.

A notice was posted on the Drug Office website on 2 August 2017 to alert the public of the drug incident.

Public urged not to buy or consume slimming products from unknown sources or of doubtful composition

On 3 August 2017, DH appealed to members of the public not to buy or consume two slimming products, one named SIN DEN SLIMMING and the other without an English name (Chinese name 「纖塑減肥胶囊」), as they were found to contain undeclared and banned drug ingredients that might be dangerous to health.

DH commenced investigation upon receipt of notification from the Hospital Authority (HA) regarding two female patients with a history of consuming the above slimming products.

Both patients attended the Accident and Emergency Department of United Christian Hospital on 2 July

2017 and 13 July 2017 respectively for palpitation and shortness of breath. Sibutramine metabolites were detected in their urine samples. They were discharged from hospital on 3 July and 13 July respectively.

According to HA's findings, which were later confirmed by the Government Laboratory, the samples of the products provided by the patients were found to contain the banned substances sibutramine and phenolphthalein. Preliminary investigations revealed that both patients purchased the slimming products from a social media network platform.

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. Phenolphthalein was once used to treat constipation, but has been banned in Hong Kong for its cancer-causing effect.

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.

A notice was posted on the Drug Office website on 3 August 2017 to alert the public of the drug incident.

DH urges public not to buy or consume product with doubtful composition

On 17 August 2017, DH urged the public not to buy or consume a product named "H.I. COFFEE" as it was found to contain an undeclared controlled ingredient.

During its market surveillance, DH purchased a sample of the above product for analysis. Test results from the Government Laboratory confirmed that the sample contained desmethyl fondenafil, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap 138).

DH officers initiated a joint operation with the Police in Mong Kok on 16 August 2017 and a woman aged 45 was arrested by the Police for illegal sale and possession of a Part 1 poison.

Desmethyl fondenafil is structurally similar to sildenafil, a prescription drug ingredient used for erectile dysfunction, and this undeclared ingredient may interact with nitrates found in some drugs such as nitroglycerin and cause a decrease in blood pressure to dangerous levels.

Drug Office has market surveillance in place to monitor products in the market. DH will continue to monitor the safety of virility products by intelligence collection, investigations and laboratory analysis.

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

A notice was posted on the Drug Office website on 17 August 2017 to alert the public of the drug incident.

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

On 21 August 2017, DH appealed to the public not to buy or consume five slimming products as they were found to contain an undeclared and banned drug ingredient that might be dangerous to health. The products are:

1. Super Slimming Herb;
2. 7 Days Slim hip & Legs;
3. DETOXI SLIM Fast Slimming Capsules;
4. MAX Slim; and
5. Slim Perfect Legs.

Acting upon a public complaint, samples of the above products were purchased from an Internet seller for analysis. Test results from the Government Laboratory revealed that the samples contain sibutramine.

Sibutramine is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap 138) and was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of increased cardiovascular risk.

A notice was posted on the Drug Office website on 21 August 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,
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