Drug News
藥 物 情 報

Issue Number 50

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in December 2013 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

US: Onfi (clobazam) associated with serious skin reactions

On 3 December 2013, the Food and Drug Administration (FDA) of the US warned that the anti-seizure drug Onfi (clobazam) can cause rare but serious skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can result in permanent harm and death.

FDA reviewed the FDA Adverse Event Reporting System (FAERS) database, the medical literature, and information submitted by the manufacturer (Lundbeck) of Onfi for evidence of a causal association between Onfi and the serious skin reactions. FDA identified 20 cases of SJS/TEN in FAERS. One additional case of TEN was identified in the literature. All of the cases had resulted in hospitalization, with one case resulting in blindness and one case resulted in death. These skin reactions can occur at any time during Onfi treatment. However, the likelihood of skin reactions is greater during the first 8 weeks of treatment or when Onfi is stopped and then re-started.

FDA had approved changes to the drug label to describe the risk of these serious skin reactions. Healthcare professionals are advised to closely monitor patients for signs or symptoms of SJS/ TEN, especially during the first 8 weeks of treatment or when re-introducing therapy, and discontinue use of Onfi and consider an alternate therapy at the first sign of rash, unless it is clearly not drug-related.

In Hong Kong, there is one registered pharmaceutical product containing clobazam, namely Frisium 10 Tab 10mg (HK-05574). It is a prescription only medicine indicated for the treatment of acute and chronic anxiety states and used as adjunctive therapy in patients with epilepsy not adequately stabilised with their basic medication. The Department of Health (DH) had not received any adverse reaction report in connection with clobazam so far. In view of FDA's recommendation, a letter to healthcare professionals was issued on 4 December 2013, and the matter will be discussed in the meeting of the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certificate of Clinical Trial/Medicine Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board.

Canada/Singapore: Xeloda (capecitabine) associated with severe skin reactions

On 3 December 2013, Roche in Canada informed healthcare professionals that very rare cases of severe cutaneous reactions such as SJS and TEN, in some cases with fatal outcome, had been reported during treatment with Xeloda. Xeloda should be immediately discontinued if signs and symptoms of SJS or TEN are present. The local package insert would be updated to reflect the new safety information.

On 9 December 2013, similar letter was also issued by Roche in Singapore and was reported in the Health Sciences Authority's (HSA) website. The local package insert of Xeloda would be updated to reflect the new safety information.

In Hong Kong, there are two capecitabine-containing pharmaceutical products registered, namely Xeloda 150mg tablets (HK-46233) and

Xeloda 500mg tablets (HK-46234). They are prescription only medicines registered by Roche and are indicated for treatment of colon, colorectal, gastric and breast cancer. Roche issued a Direct Healthcare Professional Communication about this on 4 November 2013 and submitted the application to change the package insert of the products by including the relevant safety information. DH had not received any adverse drug reaction in relation to Xeloda so far and will keep vigilant on any safety updates of the drug.

Singapore: Increased risk of glibenclamide-Induced severe and protracted hypoglycaemia in the elderly and renal impaired

On 4 December 2013, HSA announced that they had conducted a benefit-risk assessment of glibenclamide in consultation with endocrinologists and its Product Vigilance Advisory Committee (PVAC). The review was prompted by reports of a disproportionately higher number of hospitalisation cases due to hypoglycaemia associated with glibenclamide as compared to other sulfonylureas. Based on the review, which found an increased risk of severe and protracted hypoglycaemia associated with glibenclamide, HSA advised healthcare professionals that the use of glibenclamide should be avoided in the following patients:

- those above 60 years old,
- those with estimated glomerular filtration rate (eGFR) less than 60ml/min/1.73m^2, or
- those with serum creatinine (SrCr) above the upper limit of normal.

In Hong Kong, there are 30 registered pharmaceutical products containing glibenclamide. All the products are prescription only medicines indicated for the treatment of diabetes. DH had not received any adverse reaction report in connection with glibenclamide so far. DH will keep vigilant on any safety updates of the drug and actions taken by other overseas regulatory authorities for consideration of any action deemed necessary.

EU: Benefits of Kogenate Bayer/Helixate NexGen outweigh risks in previously untreated patients

On 6 December 2013, the European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the benefits of second generation factor VIII products Kogenate Bayer and Helixate NexGen continue to outweigh their risks in previously untreated patients with the bleeding disorder haemophilia A. This resulted from a review of the medicines which did not confirm a higher risk of developing factor VIII inhibitors against these medicines when compared with other factor VIII products.

The review by the PRAC was triggered by results from the RODIN study, as well as preliminary data from the European Haemophilia Safety and Surveillance System (EUHASS). The RODIN study looked at data from 574 previously untreated children with haemophilia A who were given different factor VIII products. About a third of all the children developed factor VIII inhibitors against their medicine, which reduces the benefit and makes bleeding more likely. This is a known risk for all factor VIII products but the authors of the study concluded that children given so-called second generation full-length recombinant factor VIII products such as Kogenate Bayer or Helixate NexGen were more likely to develop antibodies than those given a third generation recombinant product. An increase in inhibitor formation was not seen with other recombinant or plasma-derived factor VIII products.

After reviewing current available data on the development of inhibitors in previously untreated patients, the PRAC decided that these data did not support a conclusion that Kogenate Bayer or Helixate NexGen was associated with an increased risk of developing factor VIII inhibitors compared with other products. However, the product information for these medicines should be updated to reflect results from the RODIN study.

EMA announced on 20 December 2013 that the above PRAC recommendations were endorsed by its Committee on Human Medicinal Products (CHMP).

In Hong Kong, there are three Kogenate products registered by Bayer Healthcare Ltd, namely, Kogenate FS for Injection 250IU (HK-54068), 500IU (HK-54069) and 1000IU (HK-54067). These products are prescription only medicines

indicated for the treatment of classical hemophilia in which there is a demonstrated deficiency of activity of the plasma clotting factor FVIII. Helixate NexGen is not a registered pharmaceutical product in Hong Kong. DH continues to follow up with Bayer on any update of the product information based on results from the RODIN study, and will keep vigilant against any safety updates of the drug.

US: Methylphenidate associated with long-lasting erections

On 17 December 2013, FDA warned healthcare professionals that methylphenidate may in rare instances cause prolonged and sometimes painful erections known as priapism. Based on a recent review of methylphenidate products, FDA updated drug labels to include information about the rare but serious risk of priapism.

Priapism can occur in males of any age and happens when blood in the penis becomes trapped, leading to an abnormally long-lasting and sometimes painful erection. If not treated right away, priapism can lead to permanent damage to the penis. Younger males, especially those who have not yet reached puberty, may not recognize the problem or may be embarrassed to tell anyone if it occurs. Healthcare professionals are advised to talk to male patients and their caregivers to make sure they know the signs and symptoms of priapism and stress the need for immediate medical treatment should it occur.

The risk of priapism may cause some healthcare professionals to consider switching patients to the non-stimulant drug atomoxetine, another drug used to treat attention deficit hyperactivity disorder (ADHD); however, atomoxetine had also been associated with priapism in young children, teenagers, and adults. Priapism appears to be more common in patients taking atomoxetine than in those taking methylphenidate products; however, because of limitations in available information, FDA does not know how often priapism occurs in patients taking either type of product. Healthcare professionals should be cautious when considering changing patients from methylphenidate to atomoxetine.

In Hong Kong, there are 12 registered pharmaceutical products containing methylphenidate. They are prescription only medicines indicated for the treatment of ADHD. DH had not received any adverse reaction report in connection with the drug so far. In view of FDA's recommendations, a letter to healthcare professionals was issued on 18 December 2013 and the matter will be discussed in the meeting of the Registration Committee.

Singapore: Zofran (ondansetron) and dose-dependent QT interval prolongation – updated information on dosage and administration for intravenous use in elderly

On 13 December 2013, HSA announced that GlaxoSmithKline informed healthcare professionals of the updated dosage and administration information for intravenous (IV) Zofran in the management of chemotherapy and radiotherapy induced nausea and vomiting in the elderly. This update follows a previous safety communication informing healthcare professionals of dose-dependent QT prolongation associated with IV Zofran and the new dose restrictions for this product. Further analysis of the results of this study demonstrated a concentration-dependent relationship which warrants specific guidance to be put in place for repeat IV Zofran dosing and for the use of IV Zofran in elderly patients. The local package insert for Zofran has been updated to reflect the new safety information.

In Hong Kong, there are 20 registered pharmaceutical products containing ondansetron and five of them are injectable products. They are prescription only medicines used for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and prevention and treatment of postoperative nausea and vomiting. Safety alerts on ondansetron had been released by various overseas regulatory authorities which had been reported in Drug News Issue 24, 28 and 32. The Registration Committee discussed the issue in February 2012 and July 2013. The decision made by the Registration Committee in February 2012 was reported in Drug News Issue 28. In July 2013, the Registration Committee further discussed the matter and decided that the sales packs or package inserts of the injectable products should include the following safety

information:

1. *The use of a single 32mg intravenous dose of ondansetron should be avoided.*
2. *The maximum single IV dose should be 16mg infused over 15 minutes.*
3. *The 8mg IV dose followed by 1mg/hour continuous infusion should not be use.*
4. *Avoid ondansetron in patients with congenital long QT syndrome. Patients who may be at particular risk for QT prolongation with ondansetron are those with congenital long QT syndrome, electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking concomitant medications that prolong the QT interval.*
5. *Electrolyte abnormalities, such as hypokalemia or hypomagnesemia, should be corrected prior to the infusion of ondansetron.*

Besides, the certificate holder GlaxoSmithKline Limited of the brand product Zofran Injection (HK-33735) had submitted the application to change the package insert of their product to include the guidance for repeat IV Zofran dosing and for the use of IV Zofran in elderly patients. DH will keep vigilance on any safety updates of the drug and actions taken by other overseas regulatory authorities.

Singapore: Safety update on hydroxyethyl starch containing products

On 23 December 2013, HSA informed healthcare professionals on a new safety update regarding the use of hydroxyethyl starch (HES)-containing products in critically ill patients and recommends that HES-containing products should not be used in septic patients, critically ill patients, and in patients with renal failure and/or severe hepatic impairment. HES-containing products should only be used to treat hypovolaemia when crystalloids alone are not sufficient provided appropriate measures are taken to reduce potential risk. Positive fluid responsiveness must be confirmed after the administration of HES-containing products, and the lowest possible effective dose should be used. This recommendation is made in consultation with HSA PVAC based on information from reviews by the Cochrane Collaboration, and the two major regulatory agencies, which revealed increased mortality and renal injury requiring renal replacement therapy in these patients who were treated with HES-containing products.

In Hong Kong, there are six registered pharmaceutical products containing HES, namely Voluven Infusion 6% (HK-50474), Volulyte 6% Solution for Infusion (HK-58087), Tetraspan 6% Solution for Infusion (HK-56978), Tetraspan 10% Solution for Infusion (HK-56979), Hestar-200 Inj. 10% (HK-57095) and Hestar-200 Inj. 6% (HK-57096). Only 2 products, Voluven Infusion 6% and Volulyte 6% Solution for Infusion which are registered by Fresenius Kabi Hong Kong Ltd., are marketed in Hong Kong. They are indicated for the therapy and prophylaxis of hypovolaemia. Safety alerts on HES had been released by various overseas regulatory authorities which had been reported in Drug News Issue No. 44 and 48. A letter to healthcare professionals was issued on 17 June 2013. The safety issues were discussed in the meetings of the Registration Committee in July and December 2013. The decision made by the Registration Committee in July 2013 was reported in Drug News Issue 48. In December 2013, the Registration Committee further discussed the issues and decided that DH should remain vigilant on the final version of the warnings by the European Union health authority and the final legally binding decision by the European Commission for further consideration. The latest information published by HSA in this regard will also be provided to the Registration Committee for consideration.

Canada: Association of Revlimid (lenalidomide) with the risk of hepatotoxicity

On 27 December 2013, Health Canada announced new safety information regarding the risk of hepatoxicity for Revlimid (lenalidomide). Safety reviews for Revlimid noted a small increase in overall reporting of hepatic-related adverse events in the patient population exposed to lenalidomide. These reports were mostly of liver-related investigations, signs and symptoms. The reporting rate of hepatic failure, fibrosis and cirrhosis, cholestasis and jaundice as well as non-infectious hepatitis was low. There were a few cases with a fatal outcome and most were complicated by advanced malignant disease, previous or active liver disease, and multiple co-morbidities. The

mechanisms involved in the physiopathology remain unknown but a causal relationship between lenalidomide and hepatic disorders cannot be excluded.

Co-morbid conditions and other risk factors that may have contributed to the hepatic disorders include a history of hepatic and renal disorders or concurrent liver infection, or concomitant medications known to cause severe liver dysfunction such as acetaminophen. Monitoring of liver function is therefore recommended, particularly when there is a history of, or concurrent, viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction.

The new safety information had been added to the local package insert and are summarized as below:

- In multiple myeloma patients treated with Revlimid in combination with dexamethasone, the following severe cases of liver injuries have been reported: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis. Some of these cases had a fatal outcome.

- The mechanism of severe drug-induced hepatotoxicity in Revlimid exposed patients is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors.

- Liver enzymes should be monitored periodically. Revlimid should be stopped if an elevation of liver enzymes is observed. After return to baseline values, treatment at a lower dose may be considered.

In Hong Kong, there are eight registered pharmaceutical products containing lenalidomide, all under the brand name of Revlimid. All these products are prescription only medicines registered by Celgene Limited. They are indicated in combination with dexamethasone for treating multiple myeloma patients who have received at least one prior therapy. In view of the findings by Health Canada, a letter to healthcare professionals was issued on 30 December 2013, and the matter will be discussed in the meeting of the Registration Committee.

Drug Recall

Batch recall of B Braun Sodium Bicarbonate 8.4% Infusion

On 3 December 2013, DH endorsed a licensed drug wholesaler, B Braun Medical (HK) Limited (B Braun), to recall eight batches of Sodium Bicarbonate 8.4% Infusion (Registration Number: HK-28230) due to a potential quality issue. The batches under recall were: 121148021, 121838022, 122648022, 123518022, 124118082, 130568022, 131048021 and 131558022.

B Braun was conducting a voluntary recall of certain batches of the above product globally as precipitation was detected in some samples during a regular visual inspection conducted by the manufacturer. The presence of precipitation in the infusion product may cause or contribute to the development of adverse effects such as embolism. As a precautionary measure, B Braun had recalled all batches of the product that use the same stopper.

According to B Braun about 57,400 bottles of the affected batches were supplied to Hospital Authority and private hospitals, private doctors as well as exported to Macau. So far, no adverse report in relation to the product had been received by DH. DH had closely monitored the recall. A press statement was released on the same day to alert the public of the recall.

Recall of Dexasan-C Eye Drops

On 17 December 2013, DH instructed a licensed drug wholesaler, Today Pharma Company Limited (Today Pharma), to recall a batch of Dexasan-C Eye Drops (Dexasan-C) (registration number: HK-59504, batch number: AS033) from the market due to a quality issue.

Under the DH's market surveillance, samples of the above batch of Dexasan-C were taken for analysis. Upon the Government Laboratory's testing, the content of one of the active ingredients, chloramphenicol, was found to be lower than the labelled amount. The quality defect may affect the efficacy of the product. As a precautionary measure, DH instructed Today Pharma to recall the

above batch from the market.

Dexasan-C, containing drug ingredients chloramphenicol and dexamethasone, is a prescription medicine used for the treatment of eye infections and inflammation. It can only be supplied by pharmacies under the supervision of a registered pharmacist upon doctors' prescription. According to Today Pharma, 20,600 bottles of the affected batch of eye drops were imported to Hong Kong in April 2012. About 16,800 bottles have been sold to local private doctors and pharmacies while 1,100 bottles were exported to Macao. The affected batch is the only batch in the local market and it will expire by January 2014. DH had closely monitored the recall and informed the drug regulatory authority of Macao accordingly.

A press statement was released on the same day to alert the public of the recall. Members of the public who are using the product should consult their healthcare professionals if in doubt or when symptoms persist.

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 I poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part I 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.

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.

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: 2186 9845

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,
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