Drug News
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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 May 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: PRAC concludes there is no clear and consistent evidence of a difference in inhibitor development between classes of factor VIII medicines

On 5 May 2017, the European Medicines Agency (EMA) announced that EMA' s Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of factor VIII medicines to evaluate the risk of developing inhibitors in patients with haemophilia A who have not previously been treated with these medicines. Having reviewed the available evidence, PRAC concluded that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between the two classes of factor VIII medicines: those derived from plasma and those made by recombinant DNA technology.

Factor VIII is needed for blood to clot normally and is lacking in patients with haemophilia A. Factor VIII products replace the missing factor VIII and help control bleeding. However the body may develop inhibitors as a reaction to these medicines, particularly in patients starting treatment for the first time. This can block the medicines' effect, so bleeding is no longer controlled.

The review was started following publication of the SIPPET (Survey of Inhibitors in Plasma-Product Exposed Toddlers) study, which concluded that inhibitors develop more frequently in patients receiving recombinant factor VIII medicines than in those receiving plasma-derived factor VIII medicines. The review also covered other relevant studies, including interventional clinical trials and observational studies.

The studies reviewed differed in their design, patient populations and findings, and PRAC concluded that they did not provide clear evidence of a difference in the risk of inhibitor development between the two classes of factor VIII medicines.

In addition, due to the different characteristics of individual products within the two classes, PRAC considered that evaluation of the risk of inhibitor development should be at the product level instead of at the class level. The risk for each individual product will continue to be assessed as more evidence becomes available.

PRAC recommended that the prescribing information should be updated to reflect the current evidence. The update should include, as appropriate, listing of development of inhibitors as a very common side effect in previously untreated patients and as an uncommon side effect in previously treated patients. The existing warning on inhibitor development should be amended to highlight that the presence of low levels of inhibitors poses less of a risk of severe bleeding than high levels.

PRAC recommendation will now be sent to EMA's Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA's final opinion. Further details and information for patients and healthcare professionals will be published at the time of CHMP opinion.

Following PRAC's May 2017 recommendation, a marketing authorisation holder involved with this referral procedure has requested a re-examination. Upon receipt of the grounds for their request, PRAC will start a re-examination, which is

expected to conclude at PRAC meeting of 29 August – 1 September 2017.

In Hong Kong, there are 20 registered pharmaceutical products containing human coagulation factor VIII and 5 registered pharmaceutical products containing octocog alfa (a recombinant factor VIII product). All of them are prescription only medicines. Related news was previously issued by EMA, and was reported in the Drug News Issue No. 50, 61 and 79. As on 9 June 2017, the Department of Health (DH) has not received any adverse drug reaction (ADR) report related to human coagulation factor VIII and octocog alfa. DH will keep vigilant on the conclusion of PRAC's re-examination and final opinion of CHMP of EMA in response to PRAC recommendations.

Canada: Aranesp - Risk of severe skin reactions: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

On 5 May 2017, Health Canada announced that severe and life-threatening skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients treated with Aranesp (darbepoetin alfa).

Aranesp, an erythropoiesis-stimulating agent, is indicated in Canada for the treatment of anemia associated with chronic kidney disease (CKD) or anemia in cancer patients receiving chemotherapy.

As of 31 October 2016, cumulative exposure to Aranesp was estimated to be over 6 million patient-years in the post-marketing setting. The potential risk of SJS/TEN with Aranesp use was evaluated using the global safety databases. As of 5 April 2017, 11 cases of SJS and 4 cases of TEN have been reported internationally in patients treated with Aranesp. As of 5 May 2017, no Canadian cases of SJS/TEN related to Aranesp treatment have been identified.

SJS/TEN are serious life-threatening conditions that often begin with flu-like symptoms including fever, tiredness, muscle and joint pain which are followed by a widespread rash with reddening and blistering of the skin and moist lining of the mouth, eyes, nose, throat, or genital area. This often leads to peeling and shedding of the affected skin which looks like a severe burn. Patients should discuss any skin reaction with their doctor, and seek immediate medical attention if they experience any of the SJS/TEN symptoms.

Healthcare professionals are reminded to:

- discontinue Aranesp therapy immediately if a severe skin reaction occurs or SJS/TEN is suspected.
- permanently discontinue Aranesp if SJS/TEN is confirmed.

Health Canada is currently working with the manufacturer to include this safety information in the Canadian Product Monograph.

In Hong Kong, there are 12 registered pharmaceutical products containing darbepoetin alfa, and all are prescription only medicines registered by Kyowa Hakko Kirin (Hong Kong) Co., Limited. As on 9 June 2017, DH has not received any ADR report on darbepoetin alfa. In view of the above Health Canada announcement, DH issued a letter to inform local healthcare professionals to draw their attention on the above risk on 8 May 2017, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee).

US: Gadolinium-based Contrast Agents for Magnetic Resonance Imaging (MRI): No harmful effects identified with brain retention

On 22 May 2017, the United States (US) Food and Drug Administration (FDA) announced that an FDA's review has not identified adverse health effects from gadolinium retained in the brain after the use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI). All GBCAs may be associated with some gadolinium retention in the brain and other body tissues. However, because FDA identified no evidence that gadolinium retention in the brain from any of the GBCAs, including GBCAs associated with higher retention of gadolinium, is harmful, restricting GBCA use is not warranted at this time. FDA will continue to assess the safety of GBCAs and plan to have a public meeting to discuss this issue in the future.

FDA evaluated scientific publications and adverse event reports submitted. Some human and animal studies looked at GBCA use over periods longer than a year. These publications and reports show that gadolinium is retained in organs such as the brain, bones, and skin. The publications show that linear GBCAs retain more gadolinium in the brain than macrocyclic GBCAs. However, the review did not identify adverse health effects related to this brain retention.

FDA continues to assess the safety of GBCAs. FDA's National Center for Toxicological Research is conducting a study on brain retention of GBCAs in rats. Other research is also being conducted about how gadolinium is retained in the body. FDA will update the public when new information becomes available and FDA plan to have a public meeting to discuss this issue in the future.

GBCAs are intravenous drugs used in diagnostic imaging procedures to enhance the quality of magnetic resonance imaging or magnetic resonance angiography.

FDA recommendations for healthcare professionals and patients remain unchanged from July 2015 when FDA informed the public that this potential risk with GBCAs was being investigated. As is appropriate when considering the use of any medical imaging agent, healthcare professionals should limit GBCA use to circumstances in which additional information provided by the contrast agent is necessary, and assess the necessity of repetitive MRIs with GBCAs. Patients, parents, and caregivers should talk to their healthcare professionals if they have any questions or concerns about the use of GBCAs with MRIs. Retention of gadolinium is not found in other types of scanning agents used for other imaging procedures, such as iodine-based or radioisotopes.

In Hong Kong, there are eight 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 (Prefilled 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 and 87. As on 9 June 2017, DH has received seven cases of ADR in connection with GBCAs: two cases on Omniscan, three cases on Dotarem, and two cases on Gadovist. These reported ADR cases were not related to brain deposits. DH will remain vigilant on the safety updates from other overseas drug regulatory authorities on the adverse health effects of GBCAs.

UK: Finasteride: rare reports of depression and suicidal thoughts

On 24 May 2017, the Medicines and Healthcare products Regulatory Agency (MHRA) of United Kingdom (UK) advised that MHRA has received reports of depression and, in rare cases, suicidal thoughts in men taking finasteride 1 mg (Propecia) for male pattern hair loss. The public should be aware that depression is also associated with finasteride 5 mg (Proscar).

Finasteride is a 5α-reductase-type-2 inhibitor. In the 1 mg dose (Propecia), it is indicated for the treatment of male pattern hair loss (androgenetic alopecia). In the 5 mg dose (Proscar), it is indicated for the treatment and control of benign prostatic hyperplasia.

Some men have reported episodes of depressive illness in association with the use of Propecia for male pattern hair loss. Some men also reported having suicidal thoughts.

Depression and suicidal thoughts have been reported in men with and without a previous history of depression. Depressed mood has been previously recognised with Propecia. A recent review of the evidence has suggested more significant depression can occur and so the advice is being updated to reflect this.

The product information for Proscar in UK already lists depression as a possible adverse reaction and

is being updated in light of a recent review.

MHRA advised healthcare professionals of the followings:

- since finasteride has been marketed in UK, there have been a number of spontaneous ADR reports suggesting a possible link to depression, and in rare cases, suicidal thoughts
- advise patients to stop finasteride 1 mg (Propecia) immediately if they develop depression and inform a healthcare professional
- be aware that the product information for finasteride 5 mg (Proscar) already lists depression as a possible adverse reaction

Healthcare professionals are reminded that adverse reactions related to sexual function have been reported in association with finasteride. These include decreased libido, erectile dysfunction, and ejaculation disorders (such as decreased volume of ejaculate).

In Hong Kong, there are 35 registered pharmaceutical products containing finasteride, including 1mg tablets (13 products) and 5mg tablets (22 products), and they are prescription only medicines.

Related news regarding finasteride label changes on sexual adverse events was issued by US FDA and was reported in the Drug News Issue No. 30. DH issued a letter to inform local healthcare professionals to draw their attention on the above label changes in US on 13 April 2012. The matter has been discussed by the Registration Committee on 17 February 2015 and concluded that sales pack labels and/or package inserts should be updated with the new safety warnings by US FDA. As on 9 June 2017, DH has received one case of ADR in connection with finasteride products which is not related to depression, suicidal thoughts or sexual dysfunction.

In view of the more significant depression with suicidal thought with finasteride reported in the above MHRA announcement, DH issued a letter to inform local healthcare professionals to draw their attention on the above risk on 25 May 2017, and the matter will be discussed by the Registration Committee.

Singapore: New recommendations on the use of domperidone

On 26 May 2017, the Health Sciences Authority (HSA) announced that it has recently completed a re-assessment to determine if additional measures are necessary to further mitigate the cardiovascular (CV) risk associated with the use of domperidone. This follows an earlier assessment in 2012, which resulted in the strengthening of the package inserts of domperidone to include warnings of increased risk of ventricular arrhythmia (VA) and sudden cardiac death (SCD), especially in patients older than 60 years old or those taking oral doses of more than 30 mg daily. Domperidone is registered in Singapore for the treatment of dyspepsia, as well as nausea and vomiting due to various conditions.

HSA has reassessed its risk-benefit following a review of five epidemiology studies, which suggested an association with increased risk of VA and SCD. It was concluded that the benefit-risk profile of domperidone remains favourable when used appropriately for the above indications. Additional measures were recommended to mitigate the risk of cardiotoxicity, which included restricting its use in high risk patients and strengthening the CV warnings in the package insert. The update in package inserts in Singapore include new recommendations on the dosing regimen, treatment duration and the relevant safety information including contraindications.

Healthcare professionals are advised of the following, when considering the use of domperidone:

- Domperidone is contraindicated in patients with existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac disease and when co-administrated with QT-prolonging medicines or potent CYP3A4 inhibitors.
- An increased risk of cardiotoxicity was observed in patients older than 60 years.
- Domperidone should be used at the lowest effective dose for the shortest possible duration.
- In adults and children aged ≥ 12 years old weighing ≥ 35 kg, the recommended maximum oral daily dose is 30 mg, given in doses of 10 mg up to three times daily. Taking

into account the pharmacokinetic studies and bioavailability of rectal suppositories, the recommended rectal suppository dose is 30 mg twice daily.

- In children aged < 12 years old and those aged ≥ 12 years old weighing < 35 kg, the recommended dose is 0.25 mg/kg orally up to three times daily. For rectal administration, these patients may also be given 0.75 mg/kg twice daily as suppositories

In Hong Kong, there are 44 registered pharmaceutical products in oral preparations containing domperidone, and are prescription only medicines. Related news was previously issued by various overseas drug regulatory authorities and DH, and was reported in the Drug News Issue No. 29, 53, 57, 59 and 63. DH issued a letter to inform local healthcare professionals on 8 March 2012, 10 March 2014, 9 July 2014 and 23 September 2014. On 28 February 2012 and 5 May 2014, the Registration Committee discussed the matter and decided to update the sales pack labels and/or package inserts of domperidone-containing products to include the appropriate safety information related to cardiovascular risk and to tighten the control over the sale of oral domperidone products. As on 9 June 2017, DH has not received any ADR report related to domperidone. DH will remain vigilant on the safety update on domperidone by other overseas drug regulatory authorities.

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.

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.