Drug News
藥 物 情 報

Issue Number 99

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in January 2018 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: Recombinant human erythropoietins (r-HuEPOs): very rare risk of severe cutaneous adverse reactions (SCARs)

On 9 January 2018, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced very rare cases of SCARs, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in patients receiving r-HuEPOs and some cases were fatal. More severe cases were recorded with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta).

Five r-HuEPOs (with brand leaders) are authorised in UK: epoetin alfa (Eprex), darbepoetin alfa (Aranesp, a hyperglycosylated epoietin derivative), epoetin beta (NeoRecormon), epoetin zeta (Retacrit) and methoxy polyethylene glycol-epoetin beta (Mircera).

The long-acting r-HuEPO methoxy polyethylene glycol-epoetin beta (Mircera) has been associated with a risk of SJS and TEN following a case report in 2014 about a patient with anaemia in chronic renal failure who experienced severe mucosal eruptions 5 days after the first dose of Mircera. The patient improved with corrective treatment but symptoms re-occurred following a second dose. Warnings for SCARs have been present in the product information for Mircera since 2015.

A 2017 European review triggered by post-marketing reports of severe cutaneous reactions assessed all cases worldwide received up to February 2017, and identified a total of 23 reports of SJS and 14 reports of TEN with r-HuEPOs. At least 1 case of SJS and TEN was reported with each of the following erythropoietins: darbepoetin alfa, epoetin alfa, epoetin beta, and methoxy polyethylene glycol-epoetin beta. The review concluded that 8 reports of SJS and 1 case of TEN were causally associated with r-HuEPOs. More severe cases were observed with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta). No cases were identified with epoetin zeta; however, the review concluded that the risk of SCARs was a class effect with all r-HuEPOs. The review concluded that the class of r-HuEPOs is associated with a risk of SCARs, including SJS and TEN. The exact frequency of these reactions could not be calculated but they are understood to occur very rarely.

The product information of all r-HuEPOs is being updated in UK to reflect the risk of SCARs.

Healthcare professionals are advised to
- advise patients of the signs and symptoms of severe skin reactions at initiation and instruct them to stop treatment and seek immediate medical attention if they develop widespread rash and blistering; these rashes often occur following fever or flu-like symptoms
- discontinue all r-HuEPOs permanently in patients who develop SCARs such as SJS or TEN
- report all suspected adverse reactions to r-HuEPOs

In Hong Kong, there are 43 registered pharmaceutical products which are r-HuEPOs, containing epoetin alfa (11 products), epoetin beta (11), epoetin theta (5), darbepoetin alfa (7) and methoxy polyethylene glycol-epoetin beta (9). All products are prescription-only medicines. As on 5 February 2018, the Department of Health (DH) has

received 7 cases of adverse drug reaction (ADR) related to methoxy polyethylene glycol-epoetin beta, but these cases were not related to cutaneous adverse reactions. DH has not received any case of ADR related to other r-HuEPOs.

News related to risk of severe skin reactions of SJS and TEN on darbepoetin alfa was previously issued by Health Canada, and was reported in the Drug News Issue No. 91. DH issued a letter to inform local healthcare professionals to draw their attention on the above risk on 8 May 2017. In December 2017, the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee) discussed the matter and noted that application to update the product insert of darbepoetin alfa was submitted and reviewed. The updated product insert will include the safety information on the risks of SJS and TEN. In view of the above MHRA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on the class effect of SCARs on 10 January 2018. The matter will be discussed by the Registration Committee.

US: FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older

On 11 January 2018, the United States (US) Food and Drug Administration (FDA) is requiring safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18. FDA is also requiring the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the *Boxed Warning*, FDA's most prominent warning, of the drug labels for prescription cough and cold medicines containing codeine or hydrocodone.

FDA is taking this action after conducting an extensive review and convening a panel of outside experts. Both of these determined the risks of slowed or difficult breathing, misuse, abuse, addiction, overdose, and death with these medicines outweigh their benefits in patients younger than 18.

Healthcare professionals should be aware that FDA is changing the age range for which prescription opioid cough and cold medicines are indicated. These products will no longer be indicated for use in children, and their use in this age group is not recommended. Healthcare professionals should reassure parents that cough due to a cold or upper respiratory infection is self-limited and generally does not need to be treated. For those children in whom cough treatment is necessary, alternative medicines are available. These include over-the-counter (OTC) products such as dextromethorphan, as well as prescription benzonatate products.

Other *Boxed Warnings* and *Warnings and Precautions* will also be added to the label for prescription cough and cold medicines containing codeine or hydrocodone in US, to be consistent with the safety issues described in the labels of prescription opioid pain medicines.

In Hong Kong, there are 309 registered pharmaceutical products containing codeine, which is an ingredient used to relieve cough. There is no registered pharmaceutical product containing hydrocodone. News on safe use of codeine preparation had been issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 12, 34, 40, 44, 54, 65, 69, 90 and 97. DH issued letters to update local healthcare professionals to draw their attention on 12 October 2010, 16 August 2012, 7 June 2013 and 21 April 2017. As on 5 February 2018, DH has received two cases of ADR related to codeine for cough.

On 7 December 2017, the Registration Committee decided that the sales pack labels and/or package inserts of products containing codeine should include contraindication for all children younger than 12 years of age and for post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy, and other safety warnings. In view of the above FDA's announcement, DH issued a letter to inform local healthcare professionals on updated age limit and safety information on 12 January 2018. The matter will be further discussed by the Registration Committee.

Canada: OFEV® (nintedanib) - Risk of drug-induced liver injury and the need for regular monitoring of liver function

On 11 January 2018, Health Canada announced that drug-induced liver injuries (DILIs) have been reported in patients treated with OFEV®, including one fatal outcome. In most of these cases, the DILI was reversible when the dose was reduced or treatment was stopped. The majority of the cases occurred within the first three months of starting OFEV®. Therefore, particular attention is recommended during this initial period.

Cases of DILI have been observed with OFEV® treatment in the post-marketing setting since the product was launched in 2014 in Canada. The overall cumulative idiopathic pulmonary fibrosis patient exposure to OFEV® from marketing experience is estimated to be over 32,000 patient-years. As on 15 October 2017, 32 cases of DILI have been reported worldwide in patients treated with OFEV®, including one in Canada. In 24 of the 32 cases, the outcome of the DILI events was reported. In the majority (17) of these cases, the DILI event resolved when the dose was reduced or treatment was stopped. In 6 cases, the patient had not recovered at the time of reporting. One case resulted in fatal outcome.

Health Canada is working with the manufacturer to update the Canadian Product Monograph with this safety information.

Healthcare professionals are advised to monitor liver transaminases and bilirubin levels just before treatment starts, at regular intervals (e.g., monthly) during the first three months of treatment and periodically thereafter (e.g., at each patient visit) or as clinically indicated. Healthcare professionals are also reminded to reduce OFEV® dose or interrupt the therapy when the transaminase (AST or ALT) levels are greater than 3 times the upper limit of normal (ULN) and permanently discontinue OFEV® therapy if any liver test elevations are associated with clinical signs or symptoms of liver injury (such as jaundice).

In Hong Kong, there are 4 registered pharmaceutical products containing nintedanib, namely Vargatef Capsules 100mg (HK-64395), Vargatef Capsules 150mg (HK-64396), Ofev Capsules 100mg (HK-64604) and Ofev Capsules 150mg (HK-64605). All products are registered by Boehringer Ingelheim (HK) Ltd, and are prescription-only medicines. As on 5 February 2018, DH has received 3 cases of ADR related to nintedanib, but none of them was related to liver injury.

Related news was previously issued by Singapore Health Sciences Authority, and was reported in the Drug News Issue No. 98. DH issued a letter to inform local healthcare professionals to draw their attention on risk of liver injury on 13 December 2017. The matter will be discussed by the Registration Committee.

EU: Hydroxyethyl-starch (HES) solutions for infusion to be suspended – CMDh endorses PRAC recommendation

On 26 January 2018, the European Medicines Agency (EMA)'s Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed the recommendation to suspend the marketing authorisations of HES solutions for infusion across the European Union (EU). These products are used as plasma volume replacement following acute (sudden) blood loss, where treatment with alternative products known as 'crystalloids' alone is not considered to be sufficient.

The suspension is due to the fact that these medicines have continued to be used in critically ill patients and patients with sepsis despite restrictions on use in these patient populations introduced in 2013 to reduce the risk of kidney injury and death.

The review of HES solutions for infusion has been carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) which reviewed results of drug utilisation studies, together with the currently available data on benefits and risks from clinical trials and observational studies and feedback received from stakeholders and experts. Based on this review, PRAC concluded that the restrictions introduced in 2013 have not been sufficiently effective.

Safety Update

PRAC also explored the possibility of introducing additional measures to protect patients at risk but concluded that such measures would be ineffective or insufficient.

CMDh has agreed with the PRAC recommendation that, in view of the serious risks that certain patients are exposed to, HES solutions for infusion should be suspended. Alternative treatment options are available.

As the CMDh position was adopted by majority vote, the CMDh position will now be sent to the European Commission (EC), which will take an EU-wide legally binding decision.

In Hong Kong, there are 6 registered pharmaceutical products containing hydroxyethyl starch, namely Voluven Infusion 6% (HK-50474) and Volulyte 6% Solution for Infusion (HK-58087) registered by Fresenius Kabi Hong Kong Limited; Tetraspan 6% Solution for Infusion (HK-56978) and Tetraspan 10% Solution for Infusion (HK-56979) registered by B. Braun Medical (HK) Ltd; and Hestar-200 Inj. 10% (HK-57095) and Hestar-200 Inj. 6% (HK-57096) registered by Unico & Co. Related news on increased risks of death and kidney injury in critically ill patients was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 44, 48 and 50. DH issued letters to inform local healthcare professionals to draw their attention on the above risks on 17 June 2013 and 15 January 2018.

The Registration Committee discussed the matter in the meeting on 5 December 2013, and decided that DH will remain vigilant on the final version of the warnings by EU health authority and the final legally binding decision by EC for further consideration. CMDh endorsed the recommendation of PRAC and concluded that HES solutions must no longer be used to treat patients with sepsis or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality. Subsequently, EC endorsed it on 19 December 2013 for the adoption of a final legally binding decision valid throughout EU.

As on 5 February 2018, DH has not received any ADR case related to hydroxyethyl starch. In light of the above EMA's announcement, the matter will be discussed by the Registration Committee. DH will remain vigilant on any further new safety updates of hydroxyethyl starch released by overseas regulatory authorities.

Drug Recall

DH endorsed batch recall of Velcade Powder for Solution for Injection 3.5mg (HK-63741)

On 30 January 2018, DH endorsed a licensed drug wholesaler, Johnson & Johnson (Hong Kong) Ltd. (Johnson & Johnson), to recall 3 batches (Batch No.: GLZSM00, GLZSM01 and GJZT700) of Velcade Powder for Solution for Injection 3.5mg (HK-63741) from the market due to quality issue.

DH received notification from Johnson & Johnson that the manufacturer of the product in Italy found that the crimp cap of certain vials of the product may be rotating or loose. As a precautionary measure, Johnson & Johnson recalls the above affected batches.

The above product, containing bortezomib, is a prescription medicine used for treatment of multiple myeloma and mantle cell lymphoma.

According to Johnson & Johnson, 3,904 vials of the affected batches have been supplied to Hospital Authority, private hospitals and private doctors.

As on 5 February 2018, DH has not received any case of ADR in connection with the affected batches of product. Members of the public should consult healthcare professionals if in doubt or feeling unwell after using the product. A notice was posted on the Drug Office website on 30 January 2018 to alert the public of the product recall.

Drug Incident

Public urged not to buy or consume product of doubtful composition

On 18 January 2018, DH appealed to the public not to buy or consume a product (no English name, Chinese name: 虎骨特效风湿灵) as it was found to contain an undeclared controlled drug ingredient.

Acting upon intelligence, DH purchased a sample of the above product from an Internet seller for analysis. Test results from the Government Laboratory revealed that the sample contains diclofenac, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap 138).

Diclofenac is a non-steroidal anti-inflammatory drug for pain relief and its side-effects include gastrointestinal discomfort, nausea and peptic ulcers. Oral products containing diclofenac are prescription drugs and should be supplied at pharmacies under the supervision of a registered pharmacist upon a doctor's prescription.

A notice was released on the website of Drug Office on 18 January 2018 to alert the public of the drug incident.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap 137) and the maximum penalty is a $30,000 fine and one year's imprisonment for each offence.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.
Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 3904 1224

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920

Fax: 2319 6319

E-mail: adr@dh.gov.hk

Link: http://www.drugoffice.gov.hk/adr.html

Post: ***Pharmacovigilance Unit,***
Drug Office, Department of Health,
Rm 1856, 18/F, Wu Chung House,
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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.