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(IN REPLY PLEASE QUOTE THIS FILE REF.)

Dear Healthcare Professionals,

Recombinant human erythropoietins:
very rare risk of severe cutaneous adverse reactions (SCARs)

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency's (MHRA) announcement on very rare cases of severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in patients receiving recombinant human erythropoietins (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 the 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 Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (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 severe cutaneous adverse reactions (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 Feb 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 severe cutaneous adverse reactions 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 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 severe cutaneous adverse reactions such as SJS or TEN.
- report all suspected adverse reactions to HuEPOs on a Yellow Card.

Please refer to the following website in MHRA for details:

https://www.gov.uk/drug-safety-update/recombinant-human-erythropoietins-very-rare-risk-of-severe-cutaneous-adverse-reactions-scars

In Hong Kong, there are 43 registered pharmaceutical products which are recombinant human erythropoietins, 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. So far, the Department of Health (DH) has received 7 cases of adverse drug reaction related to methoxy polyethylene glycol-epoetin beta, but these cases were not related to cutaneous adverse reactions. The DH has not received any case of adverse drug reaction related to other recombinant human erythropoietins.

News related to risk of severe skin reactions of SJS and TEN on darbepoetin alfa was previously issued by Health Canada, and was posted on the Drug Office website on 6 May 2017, and letters to inform local healthcare professionals on the risk were issued by the DH on 8 May 2017. In Dec 2017, the Registration Committee of the Pharmacy and Poisons Board 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, the matter regarding the class effect of SCARs will be discussed by the Registration Committee of the Pharmacy and Poisons Board. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Joseph LEE)

for Assistant Director (Drug)