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(來函請敍明此檔案號碼) DH DO DIMC/7-30/1
(IN REPLY PLEASE QUOTE THIS FILE REF.)

3 Oct 2022

Dear Healthcare Professionals,

New recommendations for terlipressin-containing medicines in the treatment of hepatorenal syndrome

Your attention is drawn to the European Medicines Agency's (EMA) announcement that the Pharmacovigilance Risk Assessment Committee (PRAC) recommended new measures to reduce the risk of respiratory failure and sepsis when using terlipressin-containing medicines in people with type 1 hepatorenal syndrome (HRS-1).

The new measures include adding to the product information a warning to avoid terlipressin-containing medicines in patients with advanced acute-on-chronic liver disease or advanced kidney failure. Patients with breathing problems should receive treatment to manage their condition before starting terlipressin. During and after treatment, patients should be monitored for signs and symptoms of respiratory failure and infection. In addition, healthcare professionals can consider giving terlipressin-containing medicines as a continuous infusion into the vein as an alternative to giving it by bolus injection as this may reduce the risk of severe side effects.

The recommendations follow the PRAC's review of available data, including results from a clinical trial involving patients with HRS-1 which suggested that patients who were treated with terlipressin-containing medicines were more likely to experience and die from respiratory disorders within 90 days after the first dose than those who were given placebo. Although respiratory failure is a known side effect of terlipressin, the frequency of respiratory failure seen in the study was higher (11%) than previously reported in the product information. In addition, the study reported sepsis in 7% of patients in the terlipressin arm compared with none in the placebo group.

There were limitations to the data, such as differences in how terlipressin was used in the clinical trials compared to clinical practice. After considering these limitations together with other available data

and consulting an expert group composed of healthcare professionals with expertise in the field of hepatorenal syndrome, PRAC concluded that new measures are needed to ensure that the benefits of terlipressin-containing medicines continue to outweigh the risks.

Information for healthcare professionals:

- A higher than previously known risk of respiratory failure has been reported when using terlipressin-containing medicines for the treatment of HRS-1. In addition, a new risk of sepsis has been identified with the use of terlipressin-containing medicines for HRS-1.
- Terlipressin-containing medicines should be avoided in patients with advanced renal dysfunction (serum creatinine ≥ 442μmol/l (5.0 mg/dl)) and in patients with acute-on-chronic liver failure grade 3 and/or model for end-stage liver disease (MELD) score ≥39 MELD score, unless the benefits outweigh the risks.
- Patients with new onset of breathing difficulties or worsening of existing respiratory disease should be stabilized before treatment with terlipressin-containing medicines and should be closely monitored during treatment. If patients develop respiratory symptoms, a dose reduction of human albumin should be considered, if applicable. If symptoms are severe or do not resolve, terlipressin should be discontinued.
- Patients should be closely monitored for symptoms of infection.
- In addition, healthcare professionals can consider giving terlipressin-containing medicines as a continuous intravenous infusion as an alternative to bolus injection, as continuous infusion may reduce the risk of severe adverse events compared to bolus injection.

Please refer to the following website in EMA for details:
https://www.ema.europa.eu/en/news/new-recommendations-terlipressin-containing-medicines-treatment-hepatorenal-syndrome

In Hong Kong, there are 4 registered pharmaceutical products containing terlipressin. All products are prescription-only medicines. So far, the Department of Health (DH) has not received any case of adverse drug reaction related to terlipressin. Related news was previously issued by EMA, and was posted on the Drug Office website on 15 Jan 2022. In light of the above EMA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. 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 Adverse Drug Reaction 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,

(Terence MAN)
for Assistant Director (Drug)