SAFETY ALERT

DRAP SAFTEY ALERT NO. 42

Safety Alert of Risk of Respiratory Failure and Sepsis with Terlipressin.

Date: 20th of October, 2023.

Target Audience:

- Manufacturers and importers of terlipressin medicines;
- Healthcare professionals; and
- Patients, consumers or caregivers.

Background:

The Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom (UK) in March 2023 announced that the Pharmacovigilance Expert Advisory Group of the UK's Commission on Human Medicines agreed with the recommendations made as a result of EMA's review which was triggered by the CONFIRM trial findings that new measures were required to reduce the risk of respiratory failure and sepsis when terlipressin is used in patients with type 1 hepatorenal syndrome. The clinical trial found that in patients with type 1 hepatorenal syndrome, terlipressin may cause serious or fatal respiratory failure at a frequency higher than previously known and that terlipressin increases the risk of sepsis and septic shock.

Previously, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in September 2022 recommended new measures to reduce the risk of respiratory failure and sepsis when using terlipressin in people with type 1 hepatorenal syndrome (HRS-1), which is a serious kidney problem in people with advanced liver disease. The recommendations follow the PRAC's review of available data, including results from the CONFIRM clinical trial that included patients with HRS-1. Results of the trial suggested that patients who were treated with terlipressin were more likely to experience and die from respiratory disorders within 90 days after the first dose than those who were given a placebo. Although respiratory failure is a known adverse 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. The new measures include adding a warning to avoid terlipressin in patients with advanced acute-on-

chronic liver disease or advanced kidney failure, to the product information along with necessary recommendations to the patient. The PRAC recommendations were sent to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) which endorsed them and adopted its position on 10 November 2022. Furthermore, the label of Terlipressin (TERLIVAZ)- US-FDA also contains a Boxed Warning about respiratory failure.

Action in Pakistan:

The case was discussed in the 3rd meeting of PRAEC, held on the 8th of September, 2023, which decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 registration holders should include information about strict monitoring of respiratory failure and sepsis when using terlipressin in people with type 1 hepatorenal syndrome (HRS-1) in the warning and precaution section. Adding a warning to avoid terlipressin in patients with advanced acute-on-chronic liver disease or advanced kidney failure and information that patients with breathing problems should receive treatment to manage their condition before starting terlipressin-containing medicines in the prescribing information/ label of terlipressin when used in people with type 1 hepatorenal syndrome (HRS-1). Furthermore, registration holders were also advised to create a boxed warning regarding this risk.

Therapeutic Goods Affected.

Name: Terlipressin is a synthetic pituitary hormone indicated for the treatment of bleeding from dilated veins in the food pipe leading to the stomach (bleeding oesophageal varices) and for emergency treatment of type 1 hepatorenal syndrome (rapidly progressive renal failure in patients with liver cirrhosis (scarring of the liver) and ascites (fluid accumulation in the abdomen)). The advice is not relevant to the use of terlipressin for bleeding oesophageal varices.

Advice for patients.

Patients are informed that a higher than previously known risk of respiratory failure (severe breathing difficulty that may be life-threatening) has been reported when using terlipressin-containing medicines for the treatment of type 1 hepatorenal syndrome (HRS-1) (kidney problems in people with advanced liver disease). In addition, a new risk of sepsis (when bacteria and their toxins circulate in the blood leading to organ damage) has also been identified when terlipressin is used for treating this disease. Patients who have any questions or concerns should speak to their healthcare professionals.

Advice for healthcare professionals.

Healthcare professionals were advised to consider the individual benefits and risks for patients with type 1 hepatorenal syndrome when initiating terlipressin treatment, especially for those with severe renal or hepatic impairment and monitor all patients closely during terlipressin treatment. The advice is not relevant to the use of terlipressin for bleeding oesophageal varices. 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 (drip) into the vein as an alternative to giving it by bolus injection (full dose injected in one go) as this may reduce the risk of severe side effects.

Guidelines for reporting Adverse Drug Reactions (ADRs):

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) terlipressin to the National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP) through the Med Vigilance E-Reporting System available on the DRAP website. Similarly, ADRs can also be reported through Med Safety App which is available for download from the App Store (for iOS devices) and Google Play (for Android devices).

References:

- Minutes of 3rd meeting of Pharmacovigilance Risk Assessment Expert Committee.
- MHRA-UK: Terlipressin: new recommendations to reduce risks of respiratory failure and septic shock in patients with type 1 hepatorenal syndrome.
- EMA-Europe: New recommendations for terlipressin-containing medicines in the treatment of hepatorenal syndrome
- EMA-Europe: Terlipressin-containing medicinal products indicated in the treatment of hepatorenal syndrome