

Subject: Terlipressin Serious or fatal respiratory failure and sepsis/septic shock in patients with type 1 hepatorenal syndrome (type 1 HRS)

Dear Healthcare professional,

WE -FERRING Pharmaceuticals - in agreement with the Saudi FDA would like to inform you of the following:

Summary

- Terlipressin may cause serious or fatal respiratory failure in patients with type 1 hepatorenal syndrome (type 1 HRS) at a frequency higher than previously known.
- Terlipressin may increase the risk of sepsis/septic shock in patients with type 1 HRS.
- Avoid terlipressin in patients with advanced renal dysfunction (baseline serum creatinine [sCr] $\geq 442\mu\text{mol/l}$ (5.0 mg/dl)), due to reduced efficacy, increased mortality and increased risk of adverse events observed in these patients, unless the benefit is judged to outweigh the risks.
- Avoid terlipressin in patients with Acute-on-Chronic Liver Failure (ACLF) grade 3 and/or Model for End-stage Liver Disease (MELD) score ≥ 39 , due to reduced efficacy, increased mortality, and increased risk of respiratory failure observed in these patients, unless the benefit is judged to outweigh the risks.
- Stabilise patients with new onset of breathing difficulties or worsening of existing respiratory disease prior to administering the first dose of terlipressin. These patients should be closely monitored during treatment. If patients develop respiratory symptoms, dose reduction of human albumin should be considered, if used. If symptoms are severe or do not resolve, terlipressin should be discontinued.
- Closely monitor patients for signs and symptoms of infection.
- Terlipressin can be administered as a continuous intravenous (IV) infusion. Administration of terlipressin as continuous IV infusion may be associated with lower rates of severe adverse events than with administration by IV bolus.

Background on the safety concern

Terlipressin is indicated for type 1 hepatorenal syndrome (type 1 HRS) and bleeding oesophageal varices.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) completed a review of the safety of terlipressin in the treatment of type 1 HRS, following results from the CONFIRM trial¹.

CONFIRM was a randomised, double-blinded, placebo-controlled trial studying the efficacy and safety of terlipressin plus albumin which was conducted in the United States and Canada. In the trial, patients received albumin together with terlipressin.

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The trial met its primary efficacy endpoint, with 63 of 199 (32%) patients in the terlipressin arm as compared with 17 of 101 (17%) in the placebo arm achieving verified HRS reversal ($p= 0.006$). However, an additional secondary outcome of <90 days mortality did not show benefit with terlipressin. By day 90, death occurred in 101 patients (51%) in the terlipressin group and in 45 patients (45%) in the placebo group. Mortality within 90 days due to all cause respiratory disorders occurred in 22 patients (11%) in the terlipressin group and 2 patients (2%) in the placebo group. The incidence of all cause respiratory failure was higher in the terlipressin group than in the placebo group (20 patients (10%) vs. 3 patients (3%) for respiratory failure; 8 patients (4%) vs. 2 patients (2%) for acute respiratory failure). Although respiratory failure is a known side effect of terlipressin, the frequency of respiratory failure seen in the study was higher than previously reported in the product information.

In addition, the trial showed an imbalance in all cause sepsis/septic shock events. Fourteen patients (7%) in the terlipressin arm were reported with all cause serious adverse events related to sepsis and septic shock vs 0 patients (0%) in the placebo arm; 8/14 of the patients with sepsis in the terlipressin arm died due to the event. Sepsis/septic shock has not previously been associated with terlipressin and the exact mechanism is unknown.

PRAC also noted that reduced efficacy, increased mortality and increased risks of serious adverse events have been observed in clinical trials when terlipressin is used for treatment of type 1 HRS in patients with advanced renal dysfunction (baseline serum creatinine [sCr] $\geq 442\mu\text{mol/l}$ (5.0 mg/dl)) and in patients with Acute-on-Chronic Liver Failure (ACLF) grade 3. The risk of developing respiratory failure is particularly pronounced in patients with ACLF grade 3 and/or (MELD) score ≥ 39 . Despite limitations of the CONFIRM data, including the type of data (post hoc analysis) and possible differences with the EU clinical practice, the evidence is considered sufficient to support the need to introduce recommendations in the product information.

PRAC also considered data from an open-label randomised controlled trial by Cavallin et al.² which suggested that administration of terlipressin as continuous intravenous (IV) infusion is associated with lower rates of treatment-related adverse events than with administration by IV bolus injection. The difference in the rate of response to terlipressin between the continuous infusion and bolus groups was not statistically significant.

Taking into account the available data and following consultation with an expert group composed of healthcare professionals with expertise in the field of type 1 HRS, the PRAC concluded that an update of the product information is required to reduce the risk of respiratory failure and sepsis/septic shock when terlipressin is used for treatment of type 1 HRS.

The product information for GLypressin solution for injection is being updated to include a warning statement on use of terlipressin in patients with sCr ≥ 5 mg/dl and ACLF grade 3 and/or a Model for End-stage Liver Disease (MELD) score ≥ 39); information and guidance about the risk of sepsis/septic shock and respiratory failure and the alternative method of administration of terlipressin as a continuous IV infusion with a starting dose of 2 mg of terlipressin acetate/24 hours and increased to a maximum of 12 mg of terlipressin acetate/24 hours.

We hereby confirm that the leaflet of GLYPRESSIN will be updated to include the above warnings/concerns.

For reporting side effects please contact the below:

1. The National Pharmacovigilance Centre (NPC):
Fax: +966-11-205-7662
2. SFDA: Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: <https://ade.sfda.gov.sa>
3. JO0-QAME@ferring.com
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References

1. Wong F, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med. 2021 Mar 4;384(9):818-828. doi: 10.1056/NEJMoa2008290 [CONFIRM trial].
2. Cavallin M, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G, Gola E, Morando F, Stanco M, Rosi S, Sticca A, Cillo U, Angeli P. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. Hepatology. 2016 Mar;63(3):983-92.

With our best regards,
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