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

Dear Healthcare professional,

<*Local marketing authorisation holder*> in agreement with <the European Medicines Agency and> <insert the name of the regulatory authority, who have approved the communication> 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] ≥ 442µmol/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), bleeding oesophageal varices, and bleeding in connection with surgery particularly from gastrointestinal and urogenital tracts. The indications differ between the EU countries.

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 trial[1].

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.

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] ≥ 442µmol/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 <local product name> 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.

Call for reporting

Please report any suspected adverse reactions associated with the use of terlipressin in accordance with the national requirements via the national spontaneous reporting system, to:

<Details (e.g., name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

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.

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	<Local product name> (terlipressin)
Marketing authorisation holder(s)	All concerned marketing authorisation holders of terlipressin containing products with approved type 1 hepatorenal syndrome (HRS) indication. All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The letter circulated in each Member State should cover all active substance-containing products authorised in that Member State. It is encouraged that the originator marketing authorisation holder (where available) in each Member State acts as the contact point for the national competent authority, on behalf of the other concerned marketing authorisation holders in the same Member State. If no originator product is marketed in the Member State, it is encouraged that one of the concerned generic companies acts as contact point for the competent authority
Safety concern and purpose of the communication	To inform health care professionals about the increased risk of respiratory failure and sepsis/septic shock in patients with type 1 hepatorenal syndrome (HRS) treated with terlipressin
DHPC recipients	Hepatologists, nephrologists, gastroenterologists, internal medicine physicians, anaesthesiologists, intensive care specialists, liver transplantation experts, liver transplantation centres, hospital pharmacies from the ordering centres. The target group should be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	All EU member states where terlipressin is marketed and approved in the indication type 1 hepatorenal syndrome

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	29 Sep 2022
DHPC and communication plan (in English) agreed by CMDh	10 Nov 2022
Submission of translated DHPCs to the national competent authorities for review	7 calendar days from CMDh position
Agreement of translations by national competent authorities	14 calendar days from CMDh position
Dissemination of DHPC	21 calendar days from CMDh position/ 5 calendar days from EC decision (if applicable)