13 January 2022
EMA/PRAC/2204/2022

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for terlipressin-containing medicinal products with indication for treatment of hepatorenal syndrome

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1514

INN/active substance: terlipressin

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1. Background

This referral under Article 31 of Directive 2001/83/EC, concerning all terlipressin medicinal products for systemic use, was triggered in order to re-evaluate the benefit-risk balance of the approved indication of treatment of hepatorenal syndrome (HRS) considering the current scientific knowledge.

2. Questions

The marketing authorisation holders MAH(s) are requested to address the following questions:

Question 1

Concerning your terlipressin-containing medicinal product(s), please provide in the annexed table:

a) Information on type of marketing authorisation (legal basis), marketing- and legal status and approved indications.

b) Patient exposure by product and, if available, by indication, and also stratified by interval (before and after approval of the HRS indication) and cumulative exposure (from IBD).

c) Information on all currently approved indications, contraindications, posology and method of administration, special warnings and precautions, undesirable effects, pharmacodynamic properties and pharmacokinetic properties according to the SmPC in different EU Member States should be provided in the tabular format. Furthermore, differences between EU Member States should be described in detail and justified by data.

Question 2

In light of all the available data, and taking into consideration the results from the CONFIRM trial[1] which showed worsened outcome in the terlipressin arm compared to the placebo arm in the subgroup of patients with baseline serum creatinine level above 5 mg/dL, the MAH(s) should provide an overview of safety and efficacy of terlipressin in the treatment of HRS patients with different degrees of severity of acute kidney injury. The MAH should provide an overview if there are certain HRS patients who do not benefit from treatment.

Question 3

Based on all available sources including the literature and spontaneous reports and the information specifically from the CONFIRM trial presented in FDA documentation[2], a cumulative review of all cases of 'Haemodynamic oedema, effusions and fluid overload' (SMQ, broad) and 'respiratory failure' (SMQ, broad) should be presented. For each case, information about prior and concomitant albumin use and other risk factors should be specified.

[1] Wong F, Pappas SC, Curry MP, et al. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. N Engl J Med. 2021;384(9):818-828. doi:10.1056/NEJMoa2008290

[2] Mallinckrodt Pharmaceuticals Terlipressin Advisory Committee Briefing Document (https://www.fda.gov/media/139965/download, last accessed 13-01-2022) and FDA Briefing Document on Cardiovascular and Renal Drugs Committee Meeting, July 15, 2020 (https://www.fda.gov/media/139963/download, last accessed 13-01-2022)

Question 4

In light of all the available data, and taking into consideration the pooled results from the OT-0401[3], REVERSE[4] and CONFIRM trials, which showed a positive correlation between incidence of respiratory failure SAEs and the total prior albumin exposure, the MAH(s) should provide an overview of safety and efficacy of use of albumin prior to and concomitant with terlipressin treatment in HRS.

Question 5

The MAH(s) should provide a critical review of all available evidence in relation to the mechanism of interaction between albumin and terlipressin.

Question 6

The MAH(s) should provide a critical review of all available evidence in relation to other risk factors predisposing a worsened outcome in HRS patients treated with terlipressin including e.g. serious cardiovascular disease, respiratory deficiencies, encephalopathy, systemic inflammatory response syndrome (SIRS) and infections.

Question 7

An imbalance in sepsis/septic shock serious adverse events was also observed in the CONFIRM trial and the OT-0401 and REVERSE studies. Based on all available sources including the literature and spontaneous reports, a cumulative review of all cases of 'sepsis' (SMQ, broad) should be presented. For each case, information about other risk factors including prior and concomitant albumin use should be specified. An analysis on the possible mechanism should be discussed.

Question 8

In the CONFIRM trial, the percentage of patients who received a liver transplant within 90 days after the first dose was lower in the terlipressin group than in the placebo group (23% vs. 29%). The MAH(s) are to evaluate if treatment related adverse events (such as respiratory side effects) can be related to a decrease in transplantations. Differences between liver transplantation guidelines in EU setting and US setting should be discussed.

Question 9

The MAH(s) should provide an overview of safety and efficacy of bolus infusion compared to continuous infusion of terlipressin use in HRS patients.

Question 10

The MAH(s) should provide proposals and justifications for any risk minimisation measures (including changes to the SmPC/PL) which may improve the safe use of terlipressin in the HRS indication. In addition, the methods for monitoring the effectiveness of the risk minimization measures should be provided.

Question 11

The MAH(s) should provide a critical appraisal of the overall impact of the above data on the benefit-risk balance of terlipressin in the HRS indication. This benefit-risk balance review should especially

[3] Sanyal AJ, Boyer T, Garcia-Tsao G, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology. 2008;134(5):1360-1368. doi:10.1053/j.gastro.2008.02.014
[4] Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin Plus Albumin Is More Effective Than Albumin Alone in Improving Renal Function in Patients With Cirrhosis and Hepatorenal Syndrome Type 1. Gastroenterology. 2016;150(7):1579-1589.e2. doi:10.1053/j.gastro.2016.02.026

focus on the associated respiratory adverse reactions as one of the major risks resulting from treatment with terlipressin.

3. Annex

Question 1

a,b)

INN	Product name	Type of marketing authorisation (legal basis)	Marketing and legal status	Indications	Estimated patient exposure[1]

[1] Expressed in patient years and stratified by Member State, by indication, and by interval and cumulative exposure. Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

c)

PI	SmPC	Main differences in SmPCs between the different EU Member States
Section 4.1 Indications		
Section 4.2 Posology and method of administration		
Section 4.3 Contraindications		
Section 4.4 Special warnings and precautions		
Section 4.8 Undesirable effects		
Section 5.1 Pharmaco-dynamic properties		
Section 5.2 Pharmaco-kinetic properties		