Annex II

Scientific conclusions

Scientific conclusions

New safety data from the CONFIRM trial (Wong et al, 2021) was identified in the last Periodic safety update report single assessment (PSUSA) procedure (PSUSA/00002905/202104) for terlipressin-containing medicinal products concluded in December 2021 by PRAC. In this trial, despite a significantly increased effect on type 1 HRS reversal in the terlipressin group (the primary efficacy endpoint), no survival benefit was seen at day 90 compared to the placebo group. By day 90, death occurred in 101 patients (51%) in the terlipressin group and in 45 patients (45%) in the placebo group. Out of the deaths reported within 90 days, 11% of patients in the terlipressin group died due to respiratory disorders compared to 2% of the patients in the placebo group. Furthermore, the incidences of respiratory failure and acute respiratory failure were higher in the terlipressin group than in the placebo group (10% vs. 3% for respiratory failure and 4% vs. 2% for acute respiratory failure). An imbalance in sepsis/septic shock serious adverse events (SAEs) was also observed (7% vs 0%).

Post hoc analysis of the CONFIRM trial showed a 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. A further investigation of patient groups and risk factors associated with an increased risk of respiratory failure and death was therefore warranted.

Administration of albumin to induce and maintain normovolaemia concomitant with terlipressin administration is recommended in cirrhotic patients with initial acute kidney injury (AKI) stadium >1a, according to the European Association for the Study of the Liver (EASL) guideline for the management of patients with decompensated cirrhosis (EASL, 2018). Albumin was accordingly used as standard-of-care treatment in the CONFIRM trial in both study arms. From the results of the CONFIRM trial, a hypothesis has been raised that the observed high incidence of respiratory dysfunction could be due to a potential pharmacodynamic interaction between albumin and terlipressin. The benefit-risk balance of the combined use of albumin and terlipressin therefore required further investigation.

The EU product information recommends bolus administration of terlipressin, and bolus administration was also used in the CONFIRM trial. A study by Cavallin et al. (2016) suggested that continuous infusion of terlipressin is associated with a better safety profile than bolus administration, thereby avoiding high peak plasma concentrations of terlipressin, and hence a possible reduction of serious adverse events including volume overload and respiratory failure. Further investigation of the evidence was warranted to clarify whether the benefit-risk balance of terlipressin in the HRS indication could be improved through an update of the recommended posology.

In the context of the above PSUSA, the PRAC considered that a thorough review in the appropriate procedure is needed for the assessment of the benefit-risk balance of terlipressin in HRS.

On 22 December 2021, in view of the above concerns, the Danish Medicines Agency therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of medicinal products containing terlipressin and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked. The scope of this procedure was limited to the type 1 HRS indication.

The PRAC adopted a recommendation on 29 September 2022 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

The benefit of terlipressin in treatment of type 1 HRS is considered established based on evidence from clinical trials and meta-analysis showing a consistent effect of terlipressin on type 1 HRS reversal compared to placebo and midodrine/octreotide. The new data from the CONFIRM trial supported the established efficacy of terlipressin in treatment of type 1 HRS on the outcome of reversal of type 1 HRS. In addition, other meta-analyses were identified with reported similar efficacy results in favour of terlipressin. However, pooled data from the Mallinckrodt studies (OT-0401, REVERSE and CONFIRM) indicated no statistical differences in survival between terlipressin and placebo at any timepoint until 90 days. Accordingly, the single meta-analysis in which CONFIRM is included, found no difference in survival between terlipressin and placebo. PRAC considered that this finding is a concern as the most relevant outcome for type 1 HRS patients is to prolong the window of opportunity for a liver transplant through an increase in survival. However, there is some level of uncertainty regarding the survival outcome, as the results differ amongst the evidence (trials and meta-analysis) reviewed, due to the heterogeneity of the studies and depending on the specific selection criteria applied in the meta-analyses. A few of the smallest randomised controlled trials (RCTs) conducted do indicate a non-significant survival benefit favouring terlipressin, whereas the largest RCTs do not. Hence, when combined and weighted according to study sizes, the survival benefit seems to disappear.

When assessing the risk factors for a reduced or non-response to terlipressin treatment, it was observed that the proportional effect of terlipressin on HRS reversal appeared reduced when used to treat patients with baseline sCr above 5 mg/dl. Moreover, in the pooled data from the studies OT-0401, REVERSE, CONFIRM, patients with baseline sCr above 5 mg/dl experienced a 2-fold increased risk of death compared to placebo after 14 days. In absolute measures, it is a 27.2% difference in mortality favouring placebo treatment, and therefore patients with advanced renal dysfunction with creatinine levels above 5 mg/dl did not benefit in the study from treatment with terlipressin. PRAC discussed the prognostic ability of the threshold (sCr above 5 mg/dl) to predict an unfavourable outcome for the individual patient and considered that patients with type 1 HRS treated with terlipressin are complex and their prognosis will most likely also depend on many other important prognostic factors including e.g. age, cause of cirrhosis (e.g. alcoholic or non-alcoholic), and comorbidities. Similarly, from the post-hoc analysis of the CONFIRM trial by Wong et al (2022), reduced efficacy and increased mortality was observed in patients with very advanced liver disease defined as ACLF grade 3. PRAC noted that these are post-hoc analyses which need to be interpreted with caution. Additionally, it was noted that the treatment decisions for individual cases of type 1 HRS should be left at the discretion of the clinician, as these patients are being treated according to their individual circumstances in an advanced expert setting. This was supported by the experts consulted by PRAC during the procedure. In line with the observations and the discussion, PRAC was of the view that the data reviewed raises concerns about the benefit and risk of terlipressin treatment in specific groups of patients, and therefore PRAC considered that a warning statement to avoid terlipressin treatment in patients with baseline sCr levels above 5 mg/dl and/or ACLF grade 3 should be implemented in the product information (SmPC 4.2 and 4.4 and respective PL sections).

The safety data assessed revealed that mortality up to Day 90 was greater in the terlipressin as compared to the placebo arm in the CONFIRM trial. Fatal AEs associated with respiratory failure, sepsis and septic shock were reported in a higher percentage of subjects in the terlipressin arm in the CONFIRM study; analyses of the pooled study data revealed similar findings. The most commonly reported respiratory AEs in the terlipressin arm were respiratory failure, dyspnoea, pulmonary oedema and pleural effusion and these events were reported at a higher incidence in the terlipressin than in the placebo arm. Based on the pooled data from the 3 trials reviewed, PRAC observed that the incidence of respiratory failure and related AEs in the terlipressin arm was markedly higher than the estimated incidence according to the current SmPC section 4.8, where e.g., respiratory failure is currently listed

with frequency uncommon. PRAC therefore considered that the frequencies of the adverse reactions 'respiratory failure', 'pulmonary oedema', 'respiratory distress', 'dyspnoea' should be updated in the product information. Monitoring of the occurrence of these reactions was discussed. Experts agreed that a warning on monitoring of fluid overload is warranted in accordance with treating centres' protocols adapting treatment with albumin and diuretics accordingly, while no clearly defined protocol or tool could be identified. The product information should include wording to instruct prescribers and patients on the requirements of regular monitoring to consider during treatment (blood pressure, heart rate, oxygen saturation, serum levels of sodium and potassium, as well as fluid balance) and the particular care required in the management of patients with cardiovascular or pulmonary disease. Additionally, instructions should be added to not start treatment with terlipressin in patients with a new onset of breathing difficulties or worsening of respiratory disease and to discontinue treatment if respiratory failure symptoms are severe or do not resolve (SmPC 4.4 and respective PL section(s)).

Risk factors for the development of respiratory events were also assessed. According to a post hoc subgroup analysis of the CONFIRM trial, the group of patients with severe reduction in liver function, in particular patients with ACLF grade 3 and MELD score $\geq$ 39, had the highest risk difference for developing respiratory failure and fluid overload-related SAEs when treated with terlipressin compared to placebo. The mechanism between severely reduced liver function and increased sensitivity to terlipressin-induced respiratory disorders is at present not clear, and the association could be confounded by other factors. PRAC noted that these are post-hoc analysis which need to be interpreted with caution. Additionally, and similarly to the conclusions regarding reduced benefit in these patient subgroups, it was noted that the treatment decisions for individual cases of type 1 HRS should be left at the discretion of the clinician, as these patients are being treated according to their individual circumstances in an advanced expert setting. This was supported by the experts consulted by PRAC during the procedure. In line with the observations and the discussion, PRAC was of the view that the data reviewed raises concerns about the risk associated with terlipressin treatment in specific groups of type 1 HRS patients, and therefore concluded there is value in the inclusion of a warning in the product information regarding the association between ACLF grade 3 and/or MELD score $\geq$39 and the development of respiratory failure and thus increased mortality (SmPC 4.4 and respective PL section(s)).

The modifying role of albumin in the terlipressin-respiratory failure association was also discussed. Patients with high serum albumin levels are presumed to be at higher risk of respiratory failure when treated with terlipressin. In the CONFIRM trial, prior albumin was used in larger doses than what is recommended in the EASL guidelines and as reported by the experts consulted in the review, which may have contributed to the above safety findings. PRAC considered that given the differences in the practice reported between US and EU and since albumin is part of the standard of care, and terlipressin effectiveness depends on albumin infusion, no measure is considered needed regarding the concomitant use of albumin. It is however relevant to strengthen the product information of terlipressin products to recommend caution when terlipressin is administered together with human albumin and consider dose reduction of human albumin in case of signs or symptoms of respiratory failure or fluid overload (SmPC 4.4 and respective PL section(s)).

Based on the imbalance of sepsis/septic shock cases between the terlipressin arm and the placebo arm in all 3 trials, the fact that the risk difference (RD) of 7% (95% CI = 3.5, 10.5) in the CONFIRM trial is statistically significant and that sepsis/septic shock is a serious event and a potential fatal complication for these patients (60% of the patients with sepsis in the CONFIRM trial died of the event), PRAC considered sepsis/septic shock an important identified risk of terlipressin that should be added to the product information as a listed adverse reaction together with a warning to prescribers and patients on these events. Additionally, the product information should include instructions for daily monitoring for any symptom suggestive of infection (SmPC 4.4 and 4.8 and respective PL sections).

The evidence on the alternative method of administration by continuous intravenous (IV) infusion was considered. The MAHs provided information of several studies[1] published in the literature investigating the effect of continuous IV infusion of terlipressin in type 1 HRS in various settings. PRAC noted that the data on the safety and efficacy of continuous infusion is limited, especially in studies comparing continuous infusion to bolus injection. Even so, based on the reviewed studies from the literature, and specifically in the largest study identified (Cavallin, 2016), continuous intravenous infusion of terlipressin shows response to treatment comparable to the intravenous bolus of terlipressin and lower adverse events rates. During clinical studies, the starting dose was 2 mg/day. If no response to treatment was observed, the dose could be escalated up to a maximum of 12 mg/day. With these dosages, the rate of treatment-related adverse events was still low. Furthermore, the overall concentration of terlipressin in the blood was lower after intravenous infusion compared to the bolus. PRAC noted that the positive outcomes of the studies have led to inclusion of the continuous infusion in the clinical treatment guidelines (EASL, 2018) and clinical practice. Of note, these results are supported also by the clinical experience reported by AHEG. The AHEG experts described that their clinical experience support the current dosing recommendations of continuous IV infusion in clinical treatment guidelines (EASL 2018), as well as the two existing national SmPC updates regarding continuous infusion as alternative to bolus infusion already carried out in Italy and Austria.

Overall, despite the limitations in the evidence as outlined, PRAC considered that continuous IV infusion of terlipressin improves the overall safety profile to an extent that is clinically significant, while efficacy is not considered affected; the lower daily dose of terlipressin combined with more stable plasma concentrations associated with continuous infusion may improve the safety profile while still achieving similar response rates. PRAC considered that the observed reduction of overall treatment-related severe AEs (as predefined by Cavallin, 2016) for continuous infusion could be extrapolated specifically to SAEs of respiratory disorders and sepsis concerned in the safety review. However, uncertainty remains if this administration method can reduce the risk of respiratory failure and sepsis compared to bolus injection. In light of the assessed data, PRAC is of view that the product information should be updated to recommend continuous infusion as an alternative to bolus administration. Additionally, clear dosing recommendations are warranted in section 4.2 of the SmPC to avoid medication errors.

A direct healthcare professional communication was also agreed, together with a communication plan, to inform relevant healthcare professionals of the new recommendations and risk minimisation measures agreed as described above.

In view of the above, the Committee considers that the benefit-risk balance of terlipressin-containing medicinal products indicated for the treatment of type 1 HRS remains favourable subject to the agreed amendments to the product information.

Grounds for PRAC recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC resulting from the evaluation of data related to pharmacovigilance for terlipressin-containing medicinal products indicated in the treatment of type 1 HRS.
- The PRAC considered the totality of the data, including the clinical data from the CONFIRM trial, the pooled data for 3 trials (OT-0401, REVERSE, CONFIRM), and the data submitted by

[1] Halimi, 2002; Angeli, 2006; Angeli, 2008; Gerbes, 2009; Cavallin, 2015; Cavallin, 2016; Arora, 2020; Kulkarni, 2022.

the MAH(s) in writing. The PRAC also considered the outcome of consultation with an ad-hoc expert group.

- The PRAC concluded, based on the available efficacy data (including data which became available since the initial marketing authorisation), that the evidence does not raise serious doubts on the established efficacy on the outcome of reversal of type 1 HRS, whereas the survival benefit remains uncertain.
- The PRAC also concluded that use of terlipressin-containing medicinal products for treatment of type 1 HRS is associated with an increased risk of respiratory failure and a risk of sepsis/septic shock. The PRAC noted the potential additive effect of concomitant use of albumin and terlipressin, as albumin itself is associated with a risk of volume overload and respiratory failure, and overall higher albumin doses were used in CONFIRM compared to the EU clinical guidelines.
- The PRAC recommended that the product information should be updated to take into consideration the current clinical knowledge on safety of terlipressin when used in the treatment of type 1 HRS with warnings and precautions regarding respiratory failure and sepsis/septic shock. The PRAC also recommended that a warning to use albumin when administered together with terlipressin with caution should be included in the product information.
- The PRAC was of the view that the data reviewed raises concerns about the benefit and the risk of terlipressin treatment in specific groups of patients, namely in patients with advanced renal dysfunction (defined by baseline sCR above 442µmol/l (5.0 mg/dl)) and severe liver disease (defined as ACLF grade 3 and/or MELD score ≥39), as the use of terlipressin in these patient groups is associated with an increased risk of mortality, reduced efficacy and increased risk of adverse events, including respiratory failure (specifically for patients with ACLF grade 3 and/or MELD score ≥39). The PRAC thus concluded that the product information should be updated to indicate that use of terlipressin in the treatment of type 1 HRS in patients with baseline sCR above 442µmol/l (5.0 mg/dl) or ACLF grade 3 and/or MELD score ≥39 should be avoided unless the healthcare professionals consider that the benefits of treatment with terlipressin outweigh the risks in the individual patient.
- The PRAC considered further evidence concerning the administration of terlipressin via continuous IV infusion, alternatively to the approved method of administration (bolus injection). Overall, while PRAC noted that the evidence available is limited, it is nevertheless indicative that continuous infusion improves the overall safety profile of terlipressin to an extent that is clinically significant, while efficacy is maintained. Therefore, as a risk minimisation measure, PRAC recommended the addition of continuous IV infusion to the product information, as an alternative method of administration.
- The PRAC also agreed on the dissemination of a direct healthcare professionals communication, together with a communication plan, to highlight the new information and the warnings relative to the identified risks added to the product information.

In view of the above, the Committee considers that the benefit-risk balance of terlipressin-containing medicinal products indicated in the treatment of type 1 HRS remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for terlipressin-containing medicinal products indicated in the treatment of type 1 HRS.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of terlipressin-containing medicinal products indicated in the treatment of type 1 HRS remains favourable subject to the amendments to the product information described above.

Therefore, the CMDh recommends the variation to the terms of the marketing authorisations for terlipressin-containing medicinal products indicated in the treatment of type 1 HRS.