NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by Denmark:

Product Name(s) in the Referring Member State, if applicable	Variquel
Active substance(s) *Please clarify name(s)*	Terlipressin
Pharmaceutical form(s) *If all pharmaceutical forms are included, state "All".* *If not all pharmaceutical forms are included, please specify the one included.*	All
Strength(s) *If all strengths are included, state "All".* *If not all strengths are included, please specify the one included.*	All
Route(s) of Administration *If all routes of administration are included, state "All".* *If not all routes of administration are included, please specify the ones included.*	All
Marketing Authorisation Holder(s) in the referring Member State	Alliance

Background
Terlipressin is a synthetic vasopressin analogue, which has constrictive effects on vascular smooth muscle, inducing splanchnic arteriolar vasoconstriction with resultant reduction in portal pressure.
In the European Union (EU), with variations between Member States, terlipressin is currently indicated for bleeding oesophageal varices (BOV), hepatorenal syndrome (HRS), and bleeding in connection with surgery particularly from gastrointestinal and urogenital tracts. Terlipressin is authorised in a total of 26 EU Member States, out of which HRS is an approved indication in 17 of the Member States. Terlipressin is available as a solution and a powder for solution - both for intravenous administration. The recommended posology

differs between the indications and Member States, both regarding dosing and the duration of treatment.

Respiratory disorder is a known risk associated with terlipressin in all indications. In the EU product information, fluid overload with pulmonary oedema, respiratory distress, respiratory failure, and respiratory arrest are listed as adverse reactions in section 4.8 with the frequency uncommon. The potential mechanism is thought to be increased pulmonary vascular congenstion, through vasoconstriction in the lungs and the effects of terlipressin on cardiac afterload and systemic venous return, which could lead to pulmonary oedema.

During the reporting period of PSUSA/00002905/202104, new significant safety information emerged from the CONFIRM trial (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); a large, prospective, multi-center, randomized, double-blinded, placebo-controlled study on the efficacy and safety of terlipressin plus albumin in 300 adults with HRS-1 randomized in a 2:1 ratio. The study is the largest terlipressin trial performed in the indication to date.

Issues to be considered

The CONFIRM trial showed that the proportion of patients who had verified reversal of HRS-1 was significantly higher with terlipressin than with placebo (32% vs. 17%. P=0.0006). As secondary outcome, the study also measured <90 days mortality. By day 90 death occurred in 101 patients (51%) in the terlipressin group and in 45 patients (45%) in the placebo group. Patients in the terlipressin group were more likely to have respiratory failure and to die from respiratory failure within 90 days after the first dose. Death within 90 days due to respiratory disorders occurred in 22 patients (11%) in the terlipressin group and 2 patients (2%) 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 (20 patients (10%) vs. 3 patients (3%) for respiratory failure; 8 patients (4%) vs. 2 patients (2%) for acute respiratory failure). The incidence of respiratory failure was higher than expected from the EU product information. These observations together raise a concern for the benefit-risk balance of terlipressin when used in the HRS indication, since the benefits observed in terms of reversal of HRS-1 seemed to be counteracted by serious adverse reactions, most notably respiratory failure.
The identified concerns are limited to use in the HRS indication.

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 is 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 (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 needs 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 is 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 referenced PSUSA, the PRAC considered that a thorough review in an appropriate procedure is needed to assess the impact of these findings on the risk -benefit balance of medicinal products containing the active substance terlipressin, when used for the indication treatment of hepatorenal syndrome.

In view of the above and the necessity to take an action at EU level, Denmark considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed Date 22/12-2021

[redacted]

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