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New recommendations for terlipressin-containing medicines in the treatment of hepatorenal syndrome

On 29 September 2022, EMA's safety committee (PRAC) recommended new measures to reduce the risk of respiratory failure (severe breathing difficulties that may be life-threatening) and sepsis (when bacteria and their toxins circulate in the blood, leading to organ damage) when using terlipressin-containing medicines in people with type 1 hepatorenal syndrome (type 1 HRS) (serious kidney problems in people with advanced liver disease).

The new measures include adding to the product information a warning to avoid using terlipressin-containing medicines in patients with advanced acute-on-chronic liver disease (liver disease that suddenly worsens) or advanced kidney failure. Patients with breathing problems should receive treatment to manage their condition before starting terlipressin-containing medicines. During and after treatment, patients should be monitored for signs and symptoms of respiratory failure and infection.

In addition, healthcare professionals can consider giving terlipressin-containing medicines as a continuous infusion (drip) into the vein as an alternative to giving it by bolus injection (full dose injected in one go) as this may reduce the risk of severe side effects.[1]

The recommendations follow the PRAC's review of available data, including results from a clinical trial[2] involving patients with type 1 HRS which suggested that patients who were treated with terlipressin-containing medicines were more likely to experience and die from respiratory disorders within 90 days after the first dose than those who were given placebo (a dummy treatment).

Although respiratory failure is a known side effect of terlipressin-containing medicines, the frequency of respiratory failure seen in the study was higher (11%) than previously reported in the product information. In addition, the study reported sepsis in 7% of patients in the terlipressin arm compared with none in the placebo group.

There were limitations to the data, such as differences in how terlipressin was used in the clinical trials compared to clinical practice. After considering these limitations together with other available data and consulting an expert group composed of healthcare professionals with expertise in the field of hepatorenal syndrome, PRAC concluded that new measures were needed to ensure that the benefits of terlipressin-containing medicines continue to outweigh the risks.

[1] Cavallin M, Piano S, Romano A, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. *Hepatology*. 2016;63(3):983-92. doi:10.1002/hep.28396
[2] 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

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The PRAC recommendations were sent to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) which endorsed them and adopted its position on 10 November 2022.

Information for patients

- A higher than previously known risk of respiratory failure (severe breathing difficulty that may be life-threatening) has been reported when using terlipressin-containing medicines for the treatment of type 1 hepatorenal syndrome (type 1 HRS) (kidney problems in people with advanced liver disease). In addition, a new risk of sepsis (when bacteria and their toxins circulate in the blood leading to organ damage) has also been identified when terlipressin-containing medicines are used for treating this disease. EMA is therefore recommending several measures to reduce these risks.
- Terlipressin-containing medicines, when used for the treatment of type 1 HRS, should be avoided in patients with advanced kidney failure and in patients with advanced acute-on-chronic liver disease, unless considered absolutely necessary.
- Patients with breathing problems should receive treatment to manage their condition before starting treatment with terlipressin-containing medicines.
- Patients should be monitored for respiratory failure and infection before and during treatment, and should be treated as needed.
- Other recommended measures include giving the medicine as a continuous infusion as an alternative to bolus injection (full dose injected in one go).
- Patients who have any questions or concerns should speak to their healthcare professional.

Information for healthcare professionals

- A higher than previously known risk of respiratory failure has been reported when using terlipressin-containing medicines for the treatment of type 1 hepatorenal syndrome (type 1 HRS). In addition, a new risk of sepsis has been identified with the use of terlipressin-containing medicines for treating this disease.
- Terlipressin-containing medicines should be avoided in patients with advanced renal dysfunction (serum creatinine ≥ 442µmol/l (5.0 mg/dl)) and in patients with acute-on-chronic liver failure grade 3 and/or model for end-stage liver disease (MELD) score ≥39 MELD score, unless the benefits outweigh the risks.
- Patients with new onset of breathing difficulties or worsening of existing respiratory disease should be stabilized before treatment with terlipressin-containing medicines and should be closely monitored during treatment. If patients develop respiratory symptoms, a dose reduction of human albumin should be considered, if applicable. If symptoms are severe or do not resolve, terlipressin-containing medicines should be discontinued.
- Patients should be closely monitored for symptoms of infection.
- In addition, healthcare professionals can consider giving terlipressin-containing medicines as a continuous intravenous infusion as an alternative to bolus injection, as continuous infusion may reduce the risk of severe adverse events compared to bolus injection.

- A direct healthcare professional communication (DHPC) will be sent in due course to healthcare professionals prescribing, dispensing or administering the medicine. The DHPC will also be published on a dedicated page on the EMA website.

More about the medicine

Terlipressin is a vasopressin analogue. This means that it works in a similar way to the natural hormone vasopressin to cause narrowing of certain blood vessels in the body, in particular those that supply the abdominal organs. In patients with type 1 HRS, increased blood pressure in the liver due to liver failure leads to widening of these blood vessels, resulting in poor blood supply to the kidneys. By narrowing the blood vessels that supply the abdominal organs, terlipressin helps to restore blood flow to the kidneys, thereby improving kidney function.

Terlipressin is available as a solution and a powder for solution - both for intravenous use.

Terlipressin-containing medicines are available in the majority of EU Member States and under a variety of names including Glypressin, Terlipressin Acetate and Variquel. In addition to being authorised for type 1 HRS, they are also authorised in several EU Member States for treating bleeding from enlarged veins in the passage between the mouth and the stomach (the oesophagus) and certain forms of bleeding associated with surgery.

More about the procedure

The review of terlipressin-containing medicines has been initiated at the request of Denmark, under Article 31 of Directive 2001/83/EC.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As terlipressin-containing medicines are all authorised nationally, the PRAC recommendations were forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which has adopted its position. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by consensus, it will be directly implemented by the Member States.