

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

14.11.2022| Circular Number P11/2022

Information on Terlipressin

- Terlipressin is a vasopressin analogue which works in the same way as 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 hepatorenal syndrome (HRS-1), increased blood pressure in the liver due to liver failure leads to widening of these blood vessels (kidney problems in people with advanced liver disease). This causes an imbalance in the blood circulation, 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.

The following products are authorised via national procedure.

Active Ingredients	Product Name	Pharmaceutical Form	Classification	Authorisation Number	MAH/license holder
Terlipressin Acetate 0.2 milligram(s)/ millilitre	Terlipressinacetate EVER Pharma 0.2mg/ml Solution for Injection	Solution for injection	POM	AA729/22201	Cherubino Limited
Terlipressin Acetate 0.2 milligram(s)/ millilitre	Variquel 1mg powder and solvent for solution for injection	Powder and solvent for solution for injection	POM	AA565/28402	Central Procurement & Supplies Unit
Terlipressin Acetate 0.1 milligram(s)/ millilitre	Remestyp 1.0 mg solution for injection	Solution for injection	POM	AA565/84401	Central Procurement & Supplies Unit
Terlipressin Acetate 0.2 milligram(s)/ millilitre	Terlipressin acetate EVER Pharma 0.2 mg/ml solution for injection	Solution for injection	POM	AA1458/00201	EVER Valinject GmbH

Terlipressin acetate EVER Pharma 0.2 mg/ml solution for injection	TERLIPRESSIN ACETATE 0.2 milligram(s)/milli litre/solution for injection	Solution for injection	POM	AA1458/0020 1	EVER Valinject GmbH
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Information from the EMA about the safety concern

- 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 HRS-1).
- 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 new measures include adding to the product information a warning to avoid 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. During and after treatment, patients should be monitored for signs and symptoms of respiratory failure and infection.
- The recommendations follow the PRAC’s review of available data, including results from a clinical trial² involving patients with HRS-1 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, 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

- 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.

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.

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 $\geq 442\mu\text{mol/l}$ (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 MMA website.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance with terlipressin. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form and sending it to: Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 **or** online to <http://www.medicinesauthority.gov.mt/adrportal> or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate

Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health.

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required).

Feedback:

We thank you for your interest and look forward to hearing your opinion.

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Medicines Authority
Sir Temi Żammit Buildings
Malta Life Sciences Park
San Ġwann SĠN 3000