Review of terlipressin medicines started

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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), increased blood pressure in the liver due to liver failure leads to widening of these blood vessels. 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	Classif-ication	Authorisation Number	MAH/license holder
Terlipressin Acetate 1 milligram(s)	Variquel 1mg powder and solvent for solution for injection	Powder and solvent for solution for injection	POM	AA565/28401	Central Procurement & Supplies Unit
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

Information from the EMA about the safety concern

- EMA has started a review of medicines that contain terlipressin at the request of Denmark, under Article 31 of Directive 2001/83/EC. The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which will make a set of recommendations.

- Terlipressin containing medicines are authorised in several EU countries to treat kidney problems in people with advanced liver disease (hepatorenal syndrome; HRS), as well as bleeding from enlarged veins in the passage between the mouth and the stomach (the oesophagus) and certain forms of bleeding associated with surgery.

- EMA's safety committee (PRAC) started this review due to safety concerns about results from a large clinical trial[1] involving patients with a form of HRS where kidney function declines rapidly. The results suggest that patients who were treated with terlipressin 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).

- Respiratory disorders, such as respiratory failure (severe breathing difficulties), are a known risk of these medicines. However, the frequency of respiratory failure seen in this study (10%) was higher than reported in the product information, where it is listed as uncommon (i.e., affecting up to 1% of patients). As a result of these concerns, the Danish medicines agency requested a review of the safety of terlipressin medicines in the context of their benefits when used to treat HRS.

- At present, this review does not cover the use of terlipressin for the treatment of bleeding, since no new information on safety concerns has emerged for these uses. While the review is ongoing, terlipressin can continue to be used for these indications as well as for the treatment of HRS, according to the authorised product information. EMA will communicate PRAC's recommendations once the review has concluded.

- As terlipressin-containing medicines are all authorised nationally, the PRAC recommendations will be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a 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.

[1] 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

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:

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