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Public Assessment Report

Scientific discussion

Terlipressin Altan 1 mg solution for injection (Terlipressin Acetate)

ES/H/0749/001/DC

Date: 28/07/2025

This module reflects the scientific discussion for the approval of Terlipressin Altan 1 mg solution for injection. The procedure was finalised at 20/07/2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Terlipressin Altan 1 mg solution for injection from ALTAN PHARMA Ltd.

The product is indicated for*:*

- Hemorrhages from ruptured of esophagogastric varices.
- Emergency treatment of hepatorenal syndrome type 1, defined according to the criteria of ICA (International Club of Ascites).

A comprehensive description of the indications and posology is given in the SmPC.

This national/decentralised/mutual recognition procedure concerns a *generic* application which has been granted pursuant to Article 10 (1) *X* of Directive 2001/83/EC.

The originator product is Glypressin® 1 mg powder and solvent for solution for injection by Ferring Pharmaceuticals Ltd., registered in Germany since February 20th, 1981 and the medicinal product authorised in the Union/Member State where the application is made or European reference medicinal product is Glypressin 1 mg solution for injection from Ferring S.A.U. The reference product of Terlipressin 1 mg solution for injection was authorized by the Spanish Agency on June 2010.

In this procedure the concerned member's states have been FR, NL, PL.

II. QUALITY ASPECTS

II.1 Introduction

Terlipressin 1 mg Solution for injection is presented as ampoules containing 0.12 mg/mL Terlipressin acetate solution.
Each single dose container of Terlipressin 1 mg solution for injection is packed in type I glass ampoules of 10 ml capacity, suitable for pharmaceutical use.

II.2 Drug Substance

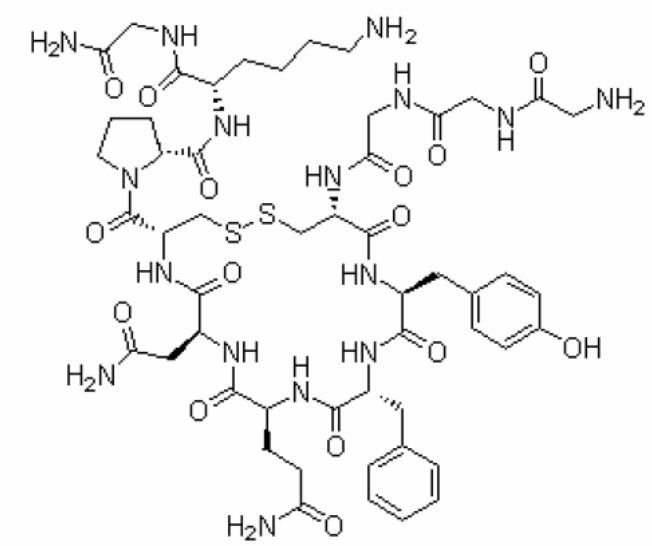
For this application, the ASMF procedure is used.

General Information

Nomenclature:

INN: Terlipressin Acetate
Chemical name: N-(N-Glycylglycyl)glycyl)-8-L-lysinevasopressin;
(2s)-1-[(4s,7s,10s,13s,16s,19s)-19-[[2-[[2-[(2-minoacetyl)amino]acetyl]amino]acetyl]amino]-13-benzyl-10-(2-carbamoylethyl)-7-(carbamoylmethyl)-16-[(4-hydroxyphenyl)methyl]-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentazacycloicosane-4-carbonyl]-n-[(1s)-5-amino-1-(carbamoylmethylcarbamoyl) pentyl]pyrrolidine-2-carboxamide.
CAS: 14636-12-5

Chemical structure:



Empirical Formula: $C_{52}H_{74}N_{16}O_{15}S_2 \cdot xC_2H_4O_2$
Molecular weight: 1227.39

General Properties:

Appearance: Terlipressin is a white or off-white hygroscopic powder.
Solubility: Soluble in water and in 1% of acetic acid solution.
pH: 5.0-7.0.
Specific Rotation:
$[\alpha]_D^{20}$ =-93.0°～-103.0°, (calculated with reference to the anhydrous, acetic acid-free substance).
Polymorphism: The sample, manufactured by Hybio, is amorphous substance.

Manufacture, process controls and characterisation

Manufacturing process is detailed. Specifications of materials used in the synthesis are sufficient and adequate. Impurity profile, including residual solvents, of these materials which can have an influence in the active substance quality, are correctly defined. Acceptance criteria for the critical steps and information on quality and control of intermediates are adequate.

Data provided can assure that the manufacturing process is correctly validated.

Specification, analytical procedures, batch analysis

Active substance specifications are considered appropriate and their limits justified. Analytical methods are correctly described and validation carried out in accordance with ICH. Batch results grant a consistent production and the proposed specifications.

Container closure system

Terlipressin is packaged in an adequate container closure system. Specifications and analytical certificates for the components of the container closure system are included. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been carried out as per ICH/CPMP guidelines. Protocol and controlled parameters are considered adequate, and methods of control stability-indicating.
Packaging material used in the stability studies is similar to that described in the dossier.
Re-test period and storage conditions are justified and can be granted.

II.3 Medicinal Product

Description of the product

Terlipressin 1 mg Solution for injection is presented as ampoules containing 0.12 mg/mL Terlipressin acetate solution.
The qualitative composition of the finished product is as follows:
Terlipressin acetate
Sodium chloride
Glacial acetic acid
Sodium acetate trihydrate
Water for injection

Each single dose container of Terlipressin 1 mg solution for injection is a type I glass ampoule of 10 mL capacity, suitable for pharmaceutical use.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions are explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.
Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.
None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are correct. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in type I glass ampoules of 10 mL capacity.
The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 18 months. After first opening, the product should be used immediately.

Storage conditions: Store between 2-8-ºC. Keep in the original package in order to protect from light. Do not freeze.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of terlipressin acetate are well known. As terlipressin acetate is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Environmental Risk Assessment (ERA)

Since Terlipressin Altan 1 mg solution for injection is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Terlipressin is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an aqueous parenteral solution the MAH did not conduct any clinical study according to the Guideline on the investigation of bioequivalence which is discussed below.

IV.2 Pharmacokinetics

Biowaiver

A bioequivalence study is not required since Terlipressin Altan 1 mg solution for injection contains the same active substance in the same quantity and concentration as the reference product Glypressin 1 mg solution for injection, and has the same indications, route of administration, dosage form and posology. The applied product also contains qualitatively the same excipients in similar amounts as the reference product. For this type of product, no

bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (version 0.2, 27 February 2018), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Terlipressin Altan 1 mg solution for injection (terlipressin acetate).

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Terlipressin Altan 1 mg solution for injection.

IV.4 Discussion on the clinical aspects

For generic applications please refer to section IV.2.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Terlipressin G.E.S. 1 mgt solution for injection (G.E.S. GENÉRICOS ESPAÑOLES LABORATORIO, S.A). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Terlipressin Altan 1 mg solution for injection is found adequate. There are no objections to the approval of Terlipressin Altan 1 mg solution for injection from a non-clinical and clinical point of view. No bioequivalence between the test and reference product is needed as the product is a parental solution at the time of administration in the same concentration as the currently authorised reference. The benefit/risk is considered positive, and the application is therefore recommended for approval.