

PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

GLYPRESSIN, solution for injection 0.1 mg/ml
Ferring B.V., the Netherlands

terlipressin acetate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.

It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 35309

21 September 2010

Pharmacotherapeutic group:	posterior pituitary lobe hormones, vasopressin and analogues
ATC code:	H01BA04
Route of administration:	intravenous
Therapeutic indication:	acute, life-threatening haemorrhages of the <i>tractus digestivus</i>
Prescription status:	prescription only
Date of authorisation in NL:	19 December 2008
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for GLYPRESSIN, solution for injection 0.1 mg/ml, from Ferring B.V. The date of authorisation was on 19 December 2008 in the Netherlands.

The product is indicated for treatment of acute, life-threatening haemorrhages of the *tractus digestivus*, in particular oesophageal variceal bleeding.

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

Terlipressin is a synthetic analogue of vasopressin, the natural hormone of the posterior lobe of the pituitary gland, differing from vasopressin in that arginine in the 8th position is substituted by lysine, and that there are three glycine residues attached to the terminal amino group of cysteine. Following intravenous injection, three glycyl moieties are enzymatically cleaved from the N-terminus to release lysine vasopressin.

This national procedure concerns a line extension of Glypressin powder for solution for injection 1 mg (NL License RVG 10302), which has been authorised in the Netherlands since 19 February 1987. The Glypressin product at issue concerns a different pharmaceutical form, *i.e.* solution for injection 0.1 mg/ml. However, the amount of active substance of the ready-to-use product remains the same (1 mg terlipressin, corresponding to 0.85 mg terlipressin acetate).

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

For the purpose of registration in the Netherlands, a full dossier has been submitted, *i.e.* including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data, in accordance with Directive 65/65/EEC, currently article 8(3) of Directive 2001/83/EC. As the product contains nearly the same amount of active substance as the registered product (after reconstitution), no new clinical studies are required. This product is a legitimate line extension to the product already marketed.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is terlipressin acetate, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white, fluffy powder which is freely soluble in water, soluble in acetic acid, and practically insoluble in acetone and ethanol.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Sufficient information has been provided on the synthesis. Also, for the starting material and solvents acceptable specifications have been adopted.

Quality control of drug substance

The drug substance specification is in line with general Ph.Eur. requirements, with additional requirements for residual solvents, bacterial endotoxins and microbiological quality. The specification is acceptable in view of the route of synthesis and the various ICH guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance

Stability data have been obtained with terlipressin drug substance samples stored at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for 36 months and at the accelerated storage conditions, $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{ RH}$ for six months.

Based on the results obtained in the stability studies, the re-test period of 24 months, stored at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, protected from light is considered justified.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

GLYPRESSIN, solution for injection 0.1 mg/ml is a clear, colourless, isotonic, sterile solution with pH between 3.5 and 4.5, and osmolarity of 303 mOsm/kg.

The solution for injection is packed in 10 ml ampoules of type I glass, containing 8.5 ml Glypressin solution.

The excipients are: sodium chloride, acetic acid (E260), sodium acetate, water for injections.

Pharmaceutical development

The development of the product is satisfactory performed and explained. The excipients used are common in the manufacture of parenteral formulations. The packaging material was chosen to ensure protection against microbial contamination. The choice of sterilisation method has been sufficiently justified. Since the drug product is a single dose preparation, no preservatives are added.

The fill volume of the 10 ml ampoule is 8.5 ml in order to give a comparable dosage of terlipressin as when using the already marketed Glypressin powder 1 mg/vial. No overage or overfill is applied.

The pharmaceutical development has been sufficiently described and explained.

Manufacturing process

The manufacturing process starts with compounding. As the solution cannot be terminally sterilized, the solution is double filtrated through a bacteria-retentive filter prior to aseptic final filling. Validation data for two production-scale batches of 2 and 10 ml fill size were included. Validation will be performed on two production-scale batches of 8.5 ml fill volume once available.

Container closure system

The ampoule complies with Ph. Eur. current edition, Hydrolytic class I glass. The primary packaging components are of standard pharmaceutical type and are compliant with pharmacopoeia requirements.

The ampoules is packed in cardboard boxes which protect from light. Adequate information on the container closure system has been provided.

Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification for the solution for injection includes tests for appearance, identity, assay, extractable volume, pH, degradation products, particulate matter, pyrogens and sterility. The release requirements are acceptable and in accordance with the Ph. Eur. Requirements for parenteralia. With respect to the impurities, the specification is in line with the requirements of ICH Q3B and limits for Glypressin powder for solution for injection (RVG 10302), and therefore toxicologically qualified. Batch analytical data for two production-scaled batches for the 8.5 ml fill size have been provided, demonstrating compliance with the specification. Batch analysis results for a third production-scale batches of 8.5 ml fill size will be provided once available.

Stability of drug product

The solution for injection has been stored at 2-8°C/ambient humidity (24 months) and 25°C/60% RH (6 months) with fill sizes of 10 and 2 ml. The 10 ml fill volume and 8 ml fill volume are both packaged in 10 ml glass ampoules and have the same head space concentration. The increase in impurities for the 2 ml and 10 ml fill volumes are comparable. The values all lie well within the limits. The stability data of 2 and 10 ml fill volumes sufficiently justify the claimed shelf life for the 8.5 ml fill volume. A shelf life of 24 months could be granted. The applicable storage conditions are 'store in a refrigerator (2°C -8°C)' and 'keep the ampoules in the outer carton in order to protect from light'.

The MAH committed to provide stability data on batches of 8.5 ml fill size.

The product is intended to be used as a bolus injection. No dilution studies were performed; therefore the terlipressin solution should not be diluted with other solutions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a line extension of Glypressin powder for solution for injection 1 mg, which is available on the Dutch market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for comparable products on the market. The approval of this product will not result in an increase in the total quantity of terlipressin acetate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Terlipressin is a well-known active substance with established efficacy and tolerability. GLYPRESSIN, solution for injection 0.1 mg/ml contains the same active substance in the same concentration as the registered powder for solution for injection after reconstitution. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the registered medicinal product. No additional clinical studies are required.

Risk management plan

Terlipressin was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of terlipressin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the registered medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC will be adapted to the text of Glypressin powder for solution for injection 1 mg (RVG 10302), for which an update is anticipated.

Readability test

The package leaflet has not been evaluated via a user consultation study, as the PIL will be adapted to the updated one for Glypressin (RVG 10302). The MAH committed to perform a readability test on the PIL once it has been established.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

GLYPRESSIN, solution for injection 0.1 mg/ml has a proven chemical-pharmaceutical quality and is a legitimate line extension of Glypressin powder for solution for injection 1 mg. Glypressin is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and will be harmonised with the previously authorised Glypressin product.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered the product a legitimate line extension to the existing Glypressin authorisation, and has therefore granted a marketing authorisation. GLYPRESSIN, solution for injection 0.1 mg/ml was authorised in the Netherlands on 19 December 2008.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The DMF will be updated in a separate variation after granting of approval of the marketing authorization of Glypressin. Subsequently the specifications will be adjusted in line with the updated DMF.

Quality - medicinal product

- The MAH committed to provide batch analysis result of a third batch of the 8.5 ml fill size.
- The MAH committed to provide stability results on two batches of 8.5 ml fill volume.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/non approval	Assessment report attached