CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Terlipressine SUN 0.1 mg/ml, solution for injection
Sun Pharmaceutical Industries Europe 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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/2412/001/DC
Registration number in the Netherlands: RVG 110384

28 March 2013

Pharmacotherapeutic group:	systemic hormonal preparations, posterior pituitary lobe hormones, vasopressin and analogues
ATC code:	H01BA04
Route of administration:	intravenous
Therapeutic indication:	bleeding oesophageal varices
Prescription status:	prescription only
Date of authorisation in NL:	15 March 2013
Concerned Member States:	Decentralised procedure with DE, DK, ES, FI, FR, IT, NO, SE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 member states have granted a marketing authorisation for Terlipressine SUN 0.1 mg/ml, solution for injection from Sun Pharmaceutical Industries Europe B.V. The date of authorisation was on 15 March 2013 in the Netherlands.

The product is indicated for bleeding oesophageal varices.

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.
The inactive pre-hormone terlipressin slowly releases bioactive lysinevasopressin. Metabolic elimination takes place concomitantly and within a period of 4-6 hours. Therefore, concentrations remain continuously above the minimal effective dose and below toxic concentrations. Terlipressin inhibits portal hypertension with simultaneous reduction of blood circulation in portal vessels. Terlipressin contracts smooth oesophageal muscle with consecutive compression of oesophageal varices

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Glypressin, which has been registered in Germany by Ferring Arzneimittel GmbH since February 1981. In the Netherlands, the marketing authorisation for Glypressin, solution for injection 0.1 mg/ml (NL License RVG 35309) was obtained on 19 December 2008 by Ferring B.V. In addition, reference is made to Glypressin/Glycylpressin authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Terlipressine SUN 0.1 mg/ml is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

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 generic application.

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 di-acetate, a well-known active substance used in EU marketed products, but not yet described in European Pharmacopoeia (Ph.Eur.*). It is a dodecapeptide with a cyclic structure due to the presence of one disulphide bridge between peptides 4 and 9. It contains eight chiral centres. It is soluble in 1M acetic acid in water. Polymorphism is not known. As the drug substance is dissolved during the manufacturing process of the drug product, its initial physical form and particle size distribution are not relevant.

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
The synthesis of terlipressin acetate is done by a twelve step process. Metal catalysts are used in the manufacturing process. Characterization data to confirm the chiral composition, the presence of the disulphide bridge, and possible formation of oligomers has been provided. A skip test for a potential genotoxic impurity has been included in the drug substance specification.

Quality control of drug substance
The drug substance specification comprises appropriate tests for the drug substance. Batch analytical data demonstrating compliance with the specification have been provided for three commercial-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches. Results of 18 months (2 batches) and 9 months (1 batch) have been provided. Based on the submitted data the proposed retest period of 12 months stored at 5 ± 3 °C is considered acceptable.

** 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
Terlipressine SUN 0.1 mg/ml contains per ml 0.12 mg terlipressin acetate, corresponding to 0.1 mg terlipressin. It is a clear and colourless solution, with pH between 3.7 and 4.2, and osmolality between 290 and 360 mOsm/kg.

The solution for infusion is packed in 10 ml clear type-I treated glass OPC (one point cut) ampoules with blue dot green band. One ampoule contains 1 mg terlipressin acetate in 8.5 ml solution for injection, corresponding to 0.85 mg terlipressin.

The excipients are: sodium acetate trihydrate, sodium chloride, glacial acetic acid (for pH adjustment), water for injections.

The information on the strength of the drug product in the SPC is based on the SPC of the UK reference product, whereas in the SPC of the Dutch innovator product the strength is given as terlipressin (as acetate).

Pharmaceutical development
The aim of the development was to mimic the reference product Glypressin. Clinical studies or bioequivalence studies have not been performed and are not required for this generic solution for injection. The same excipients have been used. Osmolality and pH are identical to the reference product. The proposed product is pharmaceutically equivalent to the reference product. The choice for sterilization by aseptic filtration is acceptable, as the active substance is not stable at the autoclavation conditions. As the drug product concerns a single-dose product, preservation is not required.

Manufacturing process
The manufacturing process concerns aqueous bulk solution preparation by dissolution of the ingredients, adjustment of the pH, sterile filtration and aseptic filling into ampoules, gassing with nitrogen, and ampoule sealing. The manufacturing process is straightforward, yet because it concerns aseptic sterilisation and filling, the process is considered a non-standard manufacturing process. Commercial-scale validation data have been provided for three batches. The validation is appropriate.

Control of excipients
The excipients are usual for this pharmaceutical form and are controlled by Ph.Eur. monographs. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identity, pH, osmolality, absorbance, transmittance, extractable volume and variation in extractable volume, particulate contamination, sterility, bacterial endotoxins, degradation products, and content terlipressin di-acetate and sodium chloride. Wider shelf-life limits are applied for individual and total degradation impurities and assay.
The methods are suitable have been adequately validated. Batch analytical data have been provided on three commercial batches and demonstrate consistent quality of the drug product.

Stability of drug product
Stability data of the product have been provided of three commercial-scale batches covering 12 months storage at long term (5°C) and accelerated conditions (25°C/60%) to support a proposed shelf-life of 24 months at 5°C. The conditions used in the stability studies are according to the ICH stability guideline. At long-term and accelerated conditions slight increases in impurities are observed. Yet, all results meet the proposed specifications at both tested conditions. The photostability results showed that the drug product is not sensitive to light. Based on the submitted data a shelf life of 24 months with the storage condition ‘Store in a refrigerator (2-8° C)’ is acceptable for the product stored in a 10 ml clear Type-I Treated glass OPC (one point cut) ampoule.
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 generic formulation of Glypressin, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is

based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of terlipressin 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.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

Terlipressine SUN 0.1 mg/ml, solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Terlipressine SUN 0.1 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan
Terlipressin was first approved in 1980, 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 post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference 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 SPC for the innovator product Glypressin is not harmonised in the EEA. The SPC approved in this decentralised procedure is in accordance with that accepted for another terlipressin product.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. During the first test round at least 90% of participants found the requested information. From the participants who found the information, the answer was found and understood ‘very easily’ or ‘easily’ by at least 80%. Based on these results, no revisions were made before starting the second test round. Based on the results of round two, an improvement to the leaflet was made by adding the explanation ‘feeling sick’ after ‘nausea’. This is considered acceptable, as the word ‘nausea’ caused difficulty for some of the respondents. Also, the type size of the headings has been adjusted to 10 points. No further changes to the PL were considered necessary. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Terlipressine SUN 0.1 mg/ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Glypressin, solution for injection 0.1 mg/ml. 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 are in agreement with other terlipressin containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Terlipressine SUN 0.1 mg/ml, solution for injection with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 5 November 2012. Terlipressine SUN 0.1 mg/ml, solution for injection was authorised in the Netherlands on 15 March 2013.

The date for the first renewal will be: 5 November 2017.

There were no post-approval commitments made during the procedure.

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
$t_{½}$	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