CBG MEB

Public Assessment Report

Scientific discussion

Desmopressine Melt Ferring 60, 120 and 240 micrograms, oral lyophilisate

(desmopressin)

NL License RVG: 116910-116912

Date: 6 July 2017

This module reflects the scientific discussion for the approval of Desmopressine Melt Ferring 60, 120 and 240 micrograms, oral lyophilisate. The marketing authorisation was granted on 16 February 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Desmopressine Melt Ferring 60, 120 and 240 micrograms, oral lyophilisate from Ferring B.V.

The product is indicated for:

- treatment of central diabetes insipidus
- treatment of primary enuresis nocturna in patients older than 5 years of age, who are capable to concentrate their urine normally.
- the symptomatic treatment of nycturia in adults associated with nocturnal polyuria.

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Minrin Melt 60, 120 and 240 micrograms, oral lyophilisate (NL License 30855-30857) which has been registered in the Nethelrands since 26 April 2005 by Ferring B.V. Ferring is also the MAH in this generic application.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

To bridge the current application to the reference products, a biowaiver has been submitted, indicating that the products at issue and the reference products are identical in qualitative and quantitative composition. The active substance used, the manufacturing process and manufacturing site for the finished dosage form are the same.

II. QUALITY ASPECTS

II.1 Introduction

Desmopressine Melt Ferring 60 micrograms is a white, round, oral lyophilisate marked with a drop shaped figure on one side.
Desmopressine Melt Ferring 120 micrograms is a white, round, oral lyophilisate marked with two drop shaped figures on one side.
Desmopressine Melt Ferring 240 micrograms is a white, round, oral lyophilisate marked with three drop shaped figures on one side.
Each unit contains desmopressin acetate equivalent to 60, 120 or 240 microgram desmopressin free base.

The oral lyophilisate is packed in aluminium/aluminium blisters.

The excipients are: gelatine (E441), mannitol (E 421), citric acid (E 330).

II.2 Drug Substance

The active substance is desmopressin, a synthetic cyclic nonapeptide, available as an acetate. It is an established active substance described in the Ph. Eur. (under the name desmopressin), the USP and Japanese Pharmacopoeia (both under the name desmopressin acetate). Desmopressin is produced as a lyophilized powder and is consequently amorphous i.e. there are no polymorphic forms.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of the MAH is the same as that of the CEP holder. The acceptance criteria are identical to or stricter than those in the Ph. Eur. monograph of desmopressin and the CEP. The specification is acceptable in view of the various European guidelines. Sufficient batch analysis data have been provided for three recent batches. It has been certified that the Ph. Eur. desmopressin Chemical Reference Standard is used to determine the peptide content in the working standard.

Stability of drug substance
The re-test period of the substance is 36 months when stored at a temperature between 2°C and 8°C. Assessment thereof was part of granting the CEP and has been performed by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies focussed on feasibility and product formulation optimisation. The packaging material chosen is usual for this (hygroscopic) type of product and acceptable.

Manufacturing process
Oral lyophilisates are obtained by freeze-drying (lyophilisation), involving division into single doses, freezing, sublimation and drying of usually aqueous, liquid or semi-solid preparations. This is regarded as a non-standard manufacturing process. The manufacturing steps are identical regardless of the unit strength being produced except for the dispensed quantities of drug substance. The manufacturing process has been adequately validated on full scale batches according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches per strength and partial data are available for additional batches.

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

Quality control of drug product
The product specification includes tests for appearance, identification, assay, degradation products, disintegration, uniformity of dosage units (mass variation), water content and microbiological quality. The release and shelf life specifications are identical except for assay, degradation products and water content. Disintegration testing is included, and the omission of dissolution testing is justified. The specifications are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on six full scale batches of the 60 and 120 micrograms strengths and four of the 240 micrograms strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for seven pilot and nine full scale batches (all strengths) stored at 25ºC/60% RH for 48 months, and 40ºC/75% RH for 6 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging, an aluminium/aluminium blister.
For all strengths of full scale batches at long term conditions the desmopressin content remains practically unchanged, whereas the content of some specified impurities/sum of degradation products and the water content increase. The water content stabilized after 36-48 months of long time storage. The same trends are visible under accelerated storage conditions. All batches complied with the specifications.
The proposed shelf-life of 48 months and storage condition ‘Store in the original package in order to protect from moisture and light’ are justified.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
It is certified by the EDQM that the drug substance desmopressin meets the criteria described in the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies', no. 1483 of the European Pharmacopoeia, current edition including supplements. It is declared that gelatin is from fish skin origin, which is not bovine so does not form a TSE risk. It is also declared that the other excipients are not from animal origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Desmopressine Melt Ferring has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Desmopressine Melt Ferring is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Minrin Melt, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

Desmopressin is a well-known active substance with established efficacy and tolerability.
No bioequivalence studies have been submitted to support the application. The MAH included a statement of identity declaring that Desmopressine Melt Ferring 60, 120 and 240 micrograms, oral lyophilisate have the same qualitative and quantitative composition in terms of the active substance, excipients and the same pharmaceutical forms, are manufactured at the same sites and follow the same manufacturing process as the reference medicinal product Minrin Melt oral lyophilsate from the same MAH. A bioavailability study is therefore not required to demonstrate bioequivalence.

IV.1 Risk Management Plan

The MAH has submitted a risk management plan, 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 Desmopressine Melt Ferring oral lyophilisate.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hyponatraemia
Important potential risks	Thrombosis Anaphylactic reaction (including allergic reactions due to fish gelatine in melt formulation)
Missing information	None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.2 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Minrin Melt. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Desmopressine Melt Ferring 60, 120 and 240 micrograms, oral lyophilisate has a proven chemical-pharmaceutical quality and is a generic form of Minrin Melt oral lyophilisate. Minrin Melt is a well-known medicinal product with an established favourable efficacy and safety profile.

A bioequivalence study was not deemed necessary, as the products at issue and the reference products are identical in qualitative and quantitative composition and manufacturing process..

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Desmopressine Melt Ferring 60, 120 and 240 micrograms, oral lyophilisate was authorised in the Netherlands on 16 February 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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