

Public Assessment Report

Scientific discussion

**Desmopressine Prolepha 60 microgram,
120 microgram and 240 microgram,
sublingual tablets
(desmopressin acetate)**

NL/H/5989/001-003/DC

Date: 26 March 2024

This module reflects the scientific discussion for the approval of Desmopressine Prolepha 60 microgram, 120 microgram and 240 microgram, sublingual tablets. The procedure was finalised at 20 June 2023 in Iceland (IS/H/0542/001-003). After a transfer on 3 October 2023, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
BE	Bioequivalence Study
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Desmopressine Prolepha 60 microgram, 120 microgram and 240 microgram, sublingual tablets from Prolepha Research B.V.

The product is indicated for:

- Treatment of central diabetes insipidus.
- Treatment of primary nocturnal enuresis in children from 5 years of age with a normal ability to concentrate urine.
- Symptomatic treatment of nocturia in adults aged below 65, associated with nocturnal polyuria, i.e. nocturnal urine production exceeding functional bladder capacity.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Minrin Melt 60 micrograms, 120 micrograms and 240 micrograms, oral lyophilisate (NL RVG 30857) which has been registered in the Netherlands by Ferring B.V. since 26 April 2005.

The concerned member state (CMS) involved in this procedure is Iceland.

Desmopressin is a structural analogue of the natural antidiuretic hormone, vasopressin.

It differs from this in that the amino group in cysteine is removed and L arginine is replaced by D arginine. This results in a significantly extended duration of action and a total lack of pressor effect in clinically current dosing.

Compared to the natural hormone, desmopressin is characterized by an increased and prolonged antidiuretic activity, while its vasopressor activity is very reduced. Desmopressin acts as a selective agonist at vasopressin V2 receptors, located primarily on the collecting duct cells of the kidney. Oral administration of a dose of 0.1 to 0.2 mg of desmopressin tablet (corresponding to 60 and 120 micrograms of oral lyophilisate) causes an antidiuretic effect which lasts approximately 8 hours with significant inter- individual variations.

II. QUALITY ASPECTS

II.1 Introduction

Desmopressine Prolepha sublingual tablets are:

60 micrograms sublingual tablet

White or almost white, round, biconvex tablet debossed with 'I' on one side and plain on other side, with 6.5 mm diameter and 2 mm thickness.

120 micrograms sublingual tablet

White or almost white, octagonal, biconvex tablet debossed with 'II' on one side and plain on other side, with 6.5 mm length/ width and 2 mm thickness.

240 micrograms sublingual tablet

White or almost white, square, biconvex tablet debossed with 'III' on one side and plain on other side with 6 mm length/ width and 2 mm thickness.

Carton box containing OPA/Al/PVC/PE-AL standard blisters or unit dose blisters with integrated desiccant layer with 10 tablets each, or HDPE bottle with PP caps.

Drug composition:

Desmopressin acetate

Excipients:

Lactose monohydrate

Maize starch

Citric acid (E 330)

Croscarmellose sodium (E 468)

Magnesium stearate (E 470b)

The excipients and container closure systems are common for this type of dosage form.

II.2 Drug Substance

Desmopressin acetate is a white or almost white fluffy powder, soluble in water, ethanol and glacial acetic acid. It does not show polymorphism. It is monographed in the European Pharmacopoeia (07:2009:0712).

Stability of drug substance

Stability studies have been conducted and the data provided is sufficient to support the proposed retest period.

II.3 Medicinal Product

Pharmaceutical development

The drug product Desmopressine Prolepha sublingual tablets was developed as a generic equivalent to Minrin Melt by Ferring from the European market. The product is intended as an immediate release product with a comparable dissolution profile to the reference and acceptable pharmaceutical stability.

Manufacturing process

Due to the low drug load (below 2%), the drug product is regarded as non-standard dosage form. The in-process controls are sufficient for immediate release tablets. The manufacturing process has been described in sufficient detail.

The manufacturing process was validated with three batches. The batch used in the bioequivalence study is part of the performed process validation. A summary of the in-process information during manufacture is provided to confirm that the proposed Desmopressin sublingual tablets can be manufactured according to the proposals in the dossier. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria.

Quality control of drug product

The proposed drug product specification is acceptable.

Analytical methods were adequately described and validated.

Batch analysis data showing compliance with the proposed release specification were provided. No risk for the presence of nitrosamine impurities in the drug product was identified.

Stability of drug product

Proposed 30 months shelf-life with special storage conditions with respect to protection from moisture for the finished product in Al/Al blisters and HDPE containers is acceptable.

The pharmaceutical quality of Desmopressine Prolepha has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

Abridged applications avoid the need for repetitive tests on animals and humans.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Desmopressine Prolepha 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

Pharmacodynamic, pharmacokinetic and toxicological properties of desmopressin are well known. As desmopressin 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. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Desmopressine Prolepha (Desmopressin) with the reference product Minrin Melt. A biowaiver is requested for the lower 60 micrograms and 120 micrograms strengths. This is acceptable as all conditions as stated in the BE Guideline are fulfilled.

IV.2 Pharmacokinetics

Bioequivalence studies

To support the application, the applicant has submitted as report one bioequivalence study.

Statement of GCP compliance is provided. A statement is provided to confirm that the bioequivalence study carried out outside the European Union meets the ethical requirements of the European Union Directive 2001/20/EC.

Design

Study was a randomised, two-treatment, four-period, two-sequence single-dose full replicate crossover study comparing Desmopressin, 240 microgram, sublingual tablets with Minrin Melt, 240 micrograms, oral lyophilisate under fasting conditions.

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} median, range) for desmopressin.

Treatment	AUC _{0-t} pg*h/ml	C _{max} pg/ml	t _{max} h
Test	390.42 \pm 465.95	91.69 \pm 88.59	1.50 (0.75 - 16.00)
Replicate Test	312.51 \pm 314.94	75.79 \pm 53.76	1.50 (0.75 - 8.00)
Pooled Test	351.87 \pm 398.28	83.82 \pm 73.50	1.50 (0.75 - 16.00)
Reference	346.30 \pm 356.07	83.70 \pm 75.67	1.50 (0.25 - 6.00)
Replicate Reference	316.67 \pm 244.49	75.74 \pm 54.67	1.50 (0.00 - 3.00)
Pooled Reference (AUC _{0-t} n=94, C _{max} n=95)	331.80 \pm 305.32	79.76 \pm 65.89	1.50 (0.00 - 6.00)
*Ratio (90% CI)	97.50 (88.83-107.02)	101.57 (92.77-111.21)	-
AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration t _{max} time for maximum plasma concentration			

*calculated based on ln-transformed data

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence study, the Desmopressin, 240 microgram, sublingual tablets is considered bioequivalent with Minrin Melt, 240 micrograms. A biowaiver is requested for the lower 60 micrograms and 120 micrograms strengths. This is acceptable as all conditions as stated in the BE Guideline are fulfilled.

IV.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

IV.4 Clinical efficacy

No new clinical efficacy studies were presented and no such studies are required for this application.

IV.5 Clinical safety

No new clinical safety studies were presented and no such studies are required for this application.

IV.6 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 desmopressin.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed. Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

IV.7 Discussion on the clinical aspects

Desmopressine Prolepha is a generic to Minrin Melt. Abridged applications avoid the need for repetitive tests on animals and humans apart from a conduction of a bioequivalence study.

The application contains an adequate review of published clinical data and the bioequivalence has been shown between applied product and with Minrin Melt.

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 language used for the purpose of user testing the PIL was English. 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

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the application for Desmopressine Prolepha, that is indicated for:

- Treatment of central diabetes insipidus.
- Treatment of primary nocturnal enuresis in children from 5 years of age with a normal ability to concentrate urine.
- Symptomatic treatment of nocturia in adults aged below 65, associated with nocturnal

polyuria, i.e. nocturnal urine production exceeding functional bladder capacity.

is considered positive and marketing authorisation is recommended.

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

There are no specific obligations and follow-up measures.

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE -
SUMMARY**

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
1041145, 1041151-2	RMS transfer from IS/H/0542/001-003 to NL/H/5989/001-003	Yes	03-10-2023	Approved	N.A.