COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Desmopressine 1A Pharma 60 micrograms, 120 micrograms and 240 micrograms, sublingual tablets

(desmopressin acetate)

NL/H/5604/001-003/DC

Date: 22 March 2024

This module reflects the scientific discussion for the approval of Desmopressine 1A Pharma 60 micrograms, 120 micrograms and 240 micrograms, sublingual tablets. The procedure was finalised at 7 June 2023. 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
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
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 Member States have granted a marketing authorisation for Desmopressine 1A Pharma 60 micrograms, 120 micrograms and 240 micrograms, sublingual tablets, from 1A Pharma GmbH.

The product is indicated for:

- Treatment of central diabetes insipidus
- Symptomatic treatment of primary nocturnal enuresis in patients from 6 years old, with a normal ability to concentrate urine.
- Symptomatic treatment of nocturia in adults, associated with nocturnal polyuria.

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

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 30855-30857) which has been registered in the Netherlands by Ferring B.V. since 26 April 2005.

The concerned member states (CMS) involved in this procedure were France and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1).

View of an interested party
In the Netherlands interested parties have the right to give their views during pending applications. An interested party took this opportunity and presented their views, in a letter in July 2022, on pending marketing authorization applications for medicinal products with desmopressin as the active substance. Following the letter, an oral hearing took place in October 2022 between the interested party and a delegation from the Dutch Medicines Evaluation Board (MEB). During the hearing, the views of the interested party were discussed. The interested party addressed certain concerns regarding the formulation (composition and disintegration time) of desmopressin tablets that may affect the clinical pharmacokinetics and pharmacodynamics, safety and efficacy of the product. Their views on the requirements for the design of the clinical trials were also presented. The views and concerns of the interested party have been carefully assessed by the MEB and taken into consideration during the assessment of this application.

II. QUALITY ASPECTS

II.1 Introduction

Desmopressine 1A Pharma is a sublingual tablet:

- Desmopressine 1A Pharma 60 micrograms is a white, round tablet, rounded on the upper and lower side, debossed with 'I' on one side and plain on the other side. Each sublingual tablet contains 67 micrograms of desmopressin acetate equivalent to 60 micrograms of desmopressin.
- Desmopressine 1A Pharma 120 micrograms is a white or almost white, octagonal tablet, rounded on the upper and lower side, debossed with 'II' on one side and plain on the other side. Each sublingual tablet contains 133 micrograms of desmopressin acetate equivalent to 120 micrograms of desmopressin.
- Desmopressine 1A Pharma 240 micrograms is a white, square tablet, rounded on the upper and lower side, debossed with 'III' on one side and plain on the other side. Each sublingual tablet contains 267 micrograms of desmopressin acetate equivalent to 240 micrograms of desmopressin.

The sublingual tablets are packed in OPA-Al-PVC-PE/Al blisters with integrated desiccant layer or HDPE containers with PP caps with integrated desiccant.

The excipients are: lactose monohydrate, maize starch, citric acid (E 330), croscarmellose, sodium (E 468) and magnesium stearate (E 470b).

II.2 Drug Substance

The active substance is desmopressin acetate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white fluffy powder. Desmopressin acetate is soluble in water, in ethanol (96 per cent) and in glacial acetic acid. Desmopressin acetate is highly hygroscopic. No polymorphism is known for the drug substance.

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 Ph.Eur.

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

Quality control of drug substance

The active substance specification is in line with the CEP and is considered adequate to control the quality. The specification meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance

No re-test period is claimed by the CEP. The MAH has adequately demonstrated that the active substance is stable for 3 years when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of packaging, formulation and manufacturing process are justified in relation to the innovator. The proposed excipients do not suppose any risk for the proposed target population. The proposed QC dissolution method is acceptable. The discriminatory power of the QC dissolution method has not been demonstrated but it is not deemed necessary in this particular case as per EMA Reflection Paper on Dissolution specification for generic solid oral immediate release products with systemic action.

One bioequivalence study with the 240 micrograms strength has been performed. The biobatches used for the study are acceptable. Comparative dissolution profiles in buffer at pH's 1.2, 4.5 and 6.8 demonstrate that the *in vitro* dissolution of both proposed and reference products is similar. For the biowaiver, dissolution test results were submitted for the strengths 60 and 120 versus 240 microgram sublingual tablets. The tests were performed at pH 6.2 and pH 7.6 (saliva pH range) at 50 rpm. The Comparison was carried out using the PhEq bootstrap program, as recommended in the EMA Q&A 3.11. The 5% lower confidence limit for the expected f2 value was above 50 in all cases. Therefore, similarity between the strengths was confirmed.

Manufacturing process

The manufacturing process consists of blending, drying, cooling, sieving, blending, compression and packing. The process has been validated according to relevant European guidelines. The manufacturing of the product is considered non-standard due to the low content of the active substance. An application for a range of batch sizes has been adequately justified considering that the manufacturing is non-standard. It is adequately justified that the proposed batch size range does not adversely impact the critical quality attributes of the finished product, in accordance with the requirements of the EMA Guideline on Process validation. Validation reports have been provided on three batches of each strength at the proposed smallest commercial batch size. A commitment and a validation protocol for the validation of the manufacturing process on three batches per strength of the highest commercial batch size have been presented and are acceptable. The

validation protocol is as per requirements of the Annex I to the EMA Guideline on Process validation for finished products.

Control of excipients

The excipients comply with Ph.Eur. requirements, except for the StarLac co-processed excipient. Nevertheless, the two components of StarLac comply with their correspondent Ph.Eur. monograph. The specification of the StarLac co-processed excipient is acceptable and the analytical methods included have been adequately described and validated.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, assay of the drug substance, uniformity of the dosage units, related substances, disintegration, dissolution and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scaled batches for each strength stored at 25°C/60% RH (12 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The batches were packed in Al/Al blister with integrated desiccant layer, or in HDPE container with PP caps and integrated desiccant. The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed on one batch of each strength demonstrating that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 2 years when stored in the original blister in order to protect from moisture. The product does not require any special temperature storage conditions.

In-use stability studies have been presented on two batches of the 60 micrograms strength packed in HDPE bottle with PP cap and integrated desiccant. All results are found within the proposed limits, and no deterioration or significant changes are detected. Therefore, an in-use shelf life in the SmPC is not considered necessary.

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

Scientific data and/or certificates of suitability issued by the EDQM for excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Desmopressine 1A Pharma 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 1A Pharma 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Desmopressin acetate 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.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Desmopressine 1A Pharma 240 micrograms, sublingual tablets (1A Pharma GmbH.,

The Netherlands) is compared with the pharmacokinetic profile of the reference product Minrin Melt 240 micrograms, oral lyophilisate (Ferring B.V., The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
- appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

As all conditions were met, a biowaiver for the lowest two strengths has been granted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 64 healthy male subjects, aged 18-43 years. Each subject received a single dose (2 x 240 micrograms) of one of the 2 desmopressin acetate formulations. Subjects had to wet the mouth by swallowing 20 ml of water before placing the tablets under the tongue. The tablets were placed under subject's tongue for 15 minutes or until dissolution (no tablets residue should remain). The tablets were not moved after placement. Subjects were instructed not to cut, crush, break, chew or swallow the tablets. They were instructed to avoid swallowing the saliva or the content. Fluid intake was not allowed 1 hour before and until 4 hours after drug administration. No food intake was allowed for at least 4 hours post-dose. There were 4 dosing periods, separated by a washout period of 7 or 8 days.

Blood samples were collected at pre-dose and at 0.08, 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14 and 16 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, patients should be advised not to eat or drink anything until the sublingual tablet is completely dissolved. As such, the fasting condition applied in the study is considered adequate.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. A replicate design was applied, to be able to widen the 90% CI for C_{max} based upon the intra-subject variability observed for the reference. Although the observed intra-subjects variability was >30%, i.e. 36.4%, the 90% CI had not to be widened as the results were within 80 – 125%.

Results

Table 1. Pooled pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of desmopressin acetate under fasted conditions.

Treatment N=95	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	352 ± 398	366 ± 454**	84 ± 74	1.5 (0.75 – 16.0)	3.5 ± 4.4
Reference	332 ± 305***	391 ± 458****	80 ± 66	1.5 (0.0 – 6.0)	84 ± 74****
***Ratio (90% CI)**	0.98 (0.89 – 1.07)	--	1.02 (0.93 – 1.11)	--	--
CV (%)	40.2	--	36.4	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values; **n=84; ***n=94; ****n=78*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Desmopressine 1A Pharma is considered bioequivalent with Minrin Melt.

The results of the bioequivalence study with 240 micrograms formulation can be extrapolated to other strengths 60 micrograms and 120 micrograms, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 1A Pharma.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.4 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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the parallelly submitted decentralized application procedure NL/H/5603/001-003/DC (Desmopressin Sandoz 60, 120 and 240 micrograms, sublingual tablets) for which a full readability test report was submitted end was selected as the parent PL. In the submitted bridging report, the applicant showed that the lay-out of the parent and daughter PL is identical. In addition, the applicant has addressed all differences on key safety messages between the parent and daughter PL. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Desmopressine 1A Pharma 60 micrograms, 120 micrograms and 240 micrograms, sublingual tablets have a proven chemical-pharmaceutical quality and are generic forms of Minrin Melt

60 micrograms, 120 micrograms and 240 micrograms, oral lyophilisate. Minrin Melt is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The application was discussed in the Board meeting of 1 June 2023 (openbaar verslag 1029e), the following was discussed:

Clinical aspects (Day 180)
The product is a sublingual tablet in strengths 60, 120 and 240 micrograms. To demonstrate similarity with the reference product, a bioequivalence study was conducted in healthy adults under fasting conditions with the strength 240 microgram. A biowaiver was requested for the strengths 60 and 120 microgram. As desmopressin is mainly absorbed sublingually, comparative disintegration and dissolution should be shown at the pH of saliva. Therefore, additional data are needed to demonstrate the similarity of the additional strengths across the pH range of saliva.
As requested, the additional data was submitted by the MAH. Based on the data, the major objection was considered resolved.

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 Desmopressine 1A Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 June 2023.

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