LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Desmopressin Orion
(desmopressin acetate)

Asp no: 2022-0605, 2022-0606, 2022-0607

This module reflects the scientific discussion for the approval of Desmopressin Orion. The procedure was finalised on 2023-10-05. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Desmopressin Orion, 60 mikrogram, 120 mikrogram, 240 mikrogram, Sublingual tablet.

The active substance is desmopressin acetate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Desmopressin Orion, 60 mikrogram, 120 mikrogram, 240 mikrogram, Sublingual tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Minirin, 60 mcg, 120 mcg and 240 mcg, respectively, oral lyophilizate, authorised in SE since 2005, with Ferring Läkemedel AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Minirin Melt, 240 mcg, oral lyophilisate, from PL with Ferring-Léčiva, a.s. as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of desmopressin are well known. As desmopressin is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Desmopressin Orion is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There were no objections to approval of Desmopressin Orion from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Desmopressin Orion (Desmopressin) with the reference product Minirin.

Pharmacokinetic properties of the active substance
Absorption: Concomitant food intake has not been studied with desmopressin lyophilised tablet, but food intake with desmopressin tablet reduces the rate of absorption and the degree of absorption by 40%. Desmopressin shows a moderate to high variation in bioavailability, both within and between individuals. Plasma concentrations of desmopressin increase in proportion to the given dose and after administration of doses of 200, 400 and 800 micrograms, C_{max} was 14, 30 and 65 pg/ml, respectively. T_{max} was reached after 0.5-2 hours.

Linearity: Dose proportional increase in exposure has seen following sublingual doses up to 60-800 micrograms.

Elimination: The estimated terminal half-life is 2.8 hours.

Study BE/20/328
Methods
This was a randomised, two-treatment, four-period, two-sequence single-dose full replicate crossover study conducted in 64 healthy volunteers, comparing Desmopressin, 240 micrograms, sublingual tablet with Minirin Melt, 240 micrograms, oral lyophilisate under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 16 hours post-dose. Plasma concentrations of desmopressin were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data

for AUC_{0-t} and C_{max}. The study was conducted between 2021-07-15 and 2021-08-08.

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

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

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test (n=48)	**390.42 ± 465.95**	**91.69 ± 88.59**	**1.50 (0.75 - 16.00)**
Replicate Test (n=47)	**312.51 ± 314.94**	**75.79 ± 53.76**	**1.50 (0.75 - 8.00)**
Pooled Test (n=95)	**351.87 ± 398.28**	**83.82 ± 73.50**	**1.50 (0.75 - 16.00)**
Reference (n=48)	**346.30 ± 356.07**	**83.70 ± 75.67**	**1.50 (0.25 - 6.00)**
Replicate Reference (n=47)	**316.67 ± 244.49**	**75.74 ± 54.67**	**1.50 (0.00 - 3.00)**
Pooled Reference (AUC_{0-t} n=94#, C_{max} n=95)	**331.80 ± 305.32**	**79.76 ± 65.89**	**1.50 (0.00 - 6.00)**
***Ratio (90% CI) (n=49)**	**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*

A biowaiver was sought for the additional strengths of 60 micrograms and 120 micrograms.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical method was adequately validated.

Absence of studies with the additional strengths of 60 micrograms and 120 micrograms is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of desmopressin is linear between 60 mg and 240 micrograms.

Based on the submitted bioequivalence study, Desmopressin Orion was considered bioequivalent with Minirin.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Orion (previously Desmopressin Kappler).

Safety specification
The MAH has submitted the version 1.1 RMP dated 2022-11-30 and proposed the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

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

Summary of the RMP
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.
The submitted Risk Management Plan, version 1.1 RMP dated 2022-11-30 was considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
At the request of the Swedish MPA;
Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Nocdurna 25, 50 micrograms oral lyophilisate SE/H/1507/01-02/DC, Desmurin 60, 120, 240 micrograms sublingual tablets DK/H/2523/01-03/DC and Buranagel DE/H/5281/01/DC.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Desmopressin Orion was found adequate. There were no objections to approval of Desmopressin Orion, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information was acceptable. The benefit/risk was considered positive, and the application was therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Desmopressin Orion, 60 mikrogram, 120 mikrogram, 240 mikrogram, Sublingual tablet was approved in the national procedure on 2023-10-06.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)