LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dapagliflozin Devatis
(dapagliflozin)

SE/H/2284/01-02/DC

This module reflects the scientific discussion for the approval of Dapagliflozin Devatis. The procedure was finalised on 2023-12-13. 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 Dapagliflozin Devatis, 5 mg, 10 mg, Film-coated tablet.

The active substance is dapagliflozin. 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 Dapagliflozin Devatis, 5 mg, 10 mg, film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Forxiga, 5 mg, film-coated tablet and Forxiga, 10 mg, film-coated tablet authorised in the EU since 2012, with AstraZeneca AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Forxiga, 10 mg, film-coated tablet from DK with AstraZeneca AB 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 dapagliflozin are well known. As dapagliflozin 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 Dapagliflozin Devatis 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 are no objections to approval of Dapagliflozin Devatis from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one (1) bioequivalence study comparing Dapagliflozin Devatis with the reference product Forxiga.

Pharmacokinetic properties of the active substance
Absorption:
Dapagliflozin has an oral bioavailability of 78 %. Following an oral dose of dapagliflozin maximal plasma concentrations occur within approximately 2 hours.

Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50% and prolonged t_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. Therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity:
The pharmacokinetics for dapagliflozin are linear. Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

Elimination:
The terminal half-life is 12.9 hours.

Study AZBE052118
Methods
This was an open label, randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 24 healthy volunteers, comparing Dapagliflozin Devatis, 10 mg, film-coated tablet with Forxiga, 10 mg, film-coated tablet under fasting conditions. Blood samples for concentration

analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of dapagliflozin were determined with an 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 29 December 2021 and 07 January 2022.

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 dapagliflozin, n=24.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**568.933 ± 136.938**	**182.149 ± 44.577**	**0.75 (0.50 - 2.50)**
Reference	**549.350 ± 153.685**	**170.803 ± 47.291**	**0.75 (0.50 - 2.50)**
***Ratio (90% CI)**	**104.28 (100.99 - 107.67)**	**107.13 (97.06 - 118.26)**	**-**
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*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 5 mg.

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 methods were adequately validated.

Absence of studies with the additional strength of 5 mg is acceptable, as all conditions for biowaiver for additional strengths, 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 dapagliflozin is linear between 0.1 mg and 500 mg.

Based on the submitted bioequivalence study, Dapagliflozin Devatis is considered bioequivalent with Forxiga.

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 Dapagliflozin Devatis.

Safety specification
Summary table of proposed safety concerns.

Summary of safety concerns	
Important identified risks	• Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	• Bladder cancer • Breast cancer • Prostate cancer • Lower limb amputation
Missing information	• Use in patients with NYHA class IV

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 submitted Risk Management Plan, version 0.1 signed 2022-08-29 is 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 RMS;
- 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
• for the content making reference to Forxiga, 5 mg, film-coated tablet and Forxiga, 10 mg, film-coated tablet within procedure EMEA/H/C/2322 (user test accepted)
• for the layout making reference to Lenalidomide Devatis 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules within procedure NL/H/4989/001-007/DC (user test accepted):
Sufficiently similar in core content, format, design and layout to allow bridging to one or more parent PILs

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Dapagliflozin Devatis, is found adequate. There are no objections to approval of Dapagliflozin Devatis, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is 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

The decentralised procedure for Dapagliflozin Devatis, 5 mg, 10 mg, Film-coated tablet was positively finalised on 2023-12-13.

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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)

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