LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Daforbis
(dapagliflozin)

SE/H/2244/01-02/DC

This module reflects the scientific discussion for the approval of Daforbis. The procedure was finalised on 2023-05-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Daforbis, 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 Daforbis, 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 HR, CY, EL, PL, RO as concerned member states (CMS).

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

Potential similarity with orphan medicinal products

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Daforbis is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Amglidia. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Amglidia in the treatment of neonatal diabetes, does not prevent the granting of the marketing authorisation of Daforbis. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation 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)
In response to CMS-RO, the applicant has provided an ERA including phase 1 assessment (with a refined PECsw calculation) and a phase II PEC/PNEC calculation where the study/data supporting the used PNEC values refers back to a dapagliflozin-ERA summary accessible on an AstraZeneca webpage. There is no reason to doubt the provided PNECs.

IV. CLINICAL ASPECTS

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

Pharmacokinetic properties of the active substance
Absorption: The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. 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. Hence, dapagliflozin can be administered with or without food.

Linearity: 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 mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects.

Study BEQ-2217-DAPA-2017
Methods
This was a single-dose, two-way crossover study conducted in 24 healthy volunteers (23 completed),

comparing Dapagliflozin, 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 48 hours post-dose. Plasma concentrations of dapagliflozin 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 08 April 2019 and 06 May 2019.

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=23.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**587.68 ± 142.88**	**99.79 ± 18.71**	**1.75 (0.50 - 3.00)**
Reference	**585.24 ± 148.76**	**97.26 ± 16.85**	**1.75 (1.00 - 4.00)**
***Ratio (90% CI)**	**100.78 (97.53-104.14)**	**102.11 (98.10-106.29)**	**-**

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 method was adequately validated.

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

Absence of studies with the additional strength of 5 mg is acceptable, as all conditions for biowaiver of 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 dapagliflozin is linear within the dose range of 0.1 mg to 500 mg.

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 an updated risk management plan, version 0.2, 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 Daforbis.

Safety specification

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 Long-term safety in the paediatric population (aged 10 years and above)

Pharmacovigilance Plan

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

The adverse reaction follow-up questionnaires (routine PhV activity beyond ADR reporting and signal detection) for the risks: diabetes ketoacidosis, bladder cancer, breast cancer, prostate cancer and lower limb amputation, are included as Annex 4 in the RMP.

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 0.2 signed 01-Dec-2022 is 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 making reference to Forxiga, EMEA/H/C/002322 and Duloxetine Mylan EMEA/H/C/003981. 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, Daforbis, is found adequate. There are no objections to approval of Daforbis, 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 Daforbis, 5 mg, 10 mg, Film-coated tablet was positively finalised on 2023-05-17.

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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)

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