COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dapagliflozin Macleods 5 mg and 10 mg, film-coated tablets (dapagliflozin)

NL/H/5356/001 & 002/DC

28 June 2022

This module reflects the scientific discussion for the approval of Dapagliflozin Macleods. The procedure was finalised at 23 February 2022. 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 Dapagliflozin Macleods 5 mg and 10 mg, film-coated tablets, from Macleods Pharma España, S.L.U.

The product is indicated for:

Type 2 diabetes mellitus
Dapagliflozin Macleods is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

Heart failure
Dapagliflozin Macleods is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

Chronic kidney disease
Dapagliflozin Macleods is indicated in adults for the treatment of chronic kidney disease.

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 Forxiga 5 mg and 10 mg film-coated tablets (EU/1/12/795) which has been authorized in the European Union via the centralised procedure since November 2012 by AstraZeneca B.V.

The concerned member states (CMS) involved in this procedure were Germany and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Dapagliflozin Macleods 5 mg film-coated tablets
Yellow coloured, round shaped, biconvex, film-coated tablets debossed with "5" on one side and plain on other side.

Dapagliflozin Macleods 10 mg film-coated tablets

Yellow coloured, diamond shaped, biconvex, film-coated tablets debossed with "10" on one side and plain on other side.

And contains as active substance 5 mg or 10 mg of dapagliflozin, respectively.

The film-coated tablets are packed in cold form laminate OPA/ Aluminium/ PVC blisters with aluminium foil.

The excipients are:

Tablet core – cellulose – microcrystalline (E460), lactose monohydrate (E473), crospovidone (E1202), sodium laurilsulfate (E487), mannitol (E421), silica – colloidal anhydrous (E551) and magnesium stearate (E572).

Film-coating – polyvinyl alcohol (E1203), macrogol 6000 (E1521), talc (E553b), titanium dioxide (E171) and yellow iron oxide (E172)

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is dapagliflozin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Dapagliflozin is an off white to white powder, it is soluble in dimethylsulfoxide and practically insoluble in cyclohexane. Dapagliflozin exhibits polymorphism and is consistently produced in its amorphous form.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>
The synthesis of the drug substance is carried out in two steps: the first step consists of the production of the intermediate in two stages, whereas the second step consists of two stages for the preparation of Dapagliflozin premix. In the last stage of the synthesis dapagliflozin is precipitated. The starting materials in the synthesis are acceptable. The need to stabilise the amorphous dapagliflozin and thus the presentation of the drug substance as a premix has been justified. The mannitol used is of Ph.Eur. quality. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The active substance specification of the DPM is in line with the specification of the ASMF holder and additional requirements for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance has been provided for three production scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the active substance for 18 months. Based on the data submitted, a retest period could be granted of 18 months when stored below 25°C (excursions permitted between 15°C and 30°C) protected from light is justified.

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 and manufacturing process are justified in relation to the innovator. The proposed QC dissolution method is acceptable, and the discriminating power of the QC dissolution method has been adequately demonstrated. The biowaiver of strength has been adequately demonstrated for the 5 mg strength at three different pHs. The comparative dissolution profiles of the reference and test biobatches have been demonstrated to be similar in the QC dissolution method and buffer at three different pHs without surfactants.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques. The description of the manufacturing process is sufficient. Process validation data on the product have been presented for three pilot scaled batches in accordance with the relevant European guidelines. A commitment to validate the manufacturing process on three commercial batches and a validation protocol have been presented by the MAH.

Control of excipients
The excipients comply with Ph.Eur. requirements, except for the in-house film-coating mixture. These specifications are acceptable.

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 description, identification of the drug substance and the colourants, water content, dissolution, uniformity of dosage units by content uniformity, related substances, residual solvents, assay 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 pilot batches from the proposed production site have been provided, demonstrating compliance with the specification. A risk evaluation concerning the presence of nitrosamine impurities in the product as per EMA/369136/2020 has been provided and is acceptable.

Stability of drug product

Stability data on the product have been provided for three pilot scaled batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the product for two years. On basis of the data submitted, a shelf life was granted of two years without any special storage condition has been proposed and is acceptable.

Photostability studies were performed in accordance with ICH Q1B recommendations and showed that the product is stable when exposed to light.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose monohydrate and magnesium stearate 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 Dapagliflozin Macleods has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH has committed to validate the manufacturing process on three commercial batches;
- The MAH has committed to present an updated validation protocol.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dapagliflozin Macleods 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 Forxiga 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

Dapagliflozin 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 Dapagliflozin Macleods 10 mg film-coated tablets (Macleods Pharma Ltd., Spain) is compared with the pharmacokinetic profile of the reference product Forxiga 10 mg film-coated tablets (AstraZeneca GmbH, Germany).

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

Biowaiver

A biowaiver of strength for the Dapagliflozin Macleods 5 mg film-coated tablets, based on the bioequivalence study of Dapagliflozin Macleods 10 mg film-coated tablets, can be granted as:

- The strengths have been manufactured by the same process and manufacturer
- The qualitative composition of the different strengths are the same
- The composition of both strengths are quantitatively proportional to dose

- The dissolution is very rapid for both strengths at several pHs. No f_2-test is required for dissolution similarity.

Bioequivalence studies

Design

An open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 21-44 years. Each subject received a single dose (10 mg) of one of the two dapagliflozin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at pre-dose and 0.08, 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 4.00, 6.00, 8.00, 12.00, 18.00, 24.00, 30.00, 36.00 and 48.00 hours after administration of the products.

The design of the study is acceptable.

Dapagliflozin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of dapagliflozin. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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.

Results

Out of a total of 24, 23 subjects were eligible for pharmacokinetic analysis. One subject was withdrawn due to an adverse event.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of dapagliflozin (10 mg) under fasted conditions.

Treatment N=22	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	587.7 ± 142.9	604.8 ± 146.7	99.8 ± 18.7	1.75 (0.50 - 3.00)
Reference	585.2 ± 148.8	598.9 ± 150.7	97.3 ± 16.9	1.75 (1.00 - 4.00)
***Ratio (90% CI)**	1.01 (0.98 – 1.04)	--	1.02 (0.98 – 1.06)	--

$AUC_{0-\infty}$	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
CI	confidence interval

**In-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Dapagliflozin Macleods is considered bioequivalent with Forxiga.

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 Dapagliflozin Macleods.

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

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

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 Forxiga. 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

The package leaflet (PL) 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 PL was English. The test consisted of a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Dapagliflozin Macleods 5 mg and 10 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Forxiga. Forxiga 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 Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dapagliflozin Macleods with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 February 2022.

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