COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Glusod 10 mg and 25 mg film-coated tablets (empagliflozin)

NL/H/5639/001-002/DC

Date: 18 December 2024

This module reflects the scientific discussion for the approval of Glusod 10 mg and 25 mg film-coated tablets. The procedure was finalised on 15 February 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Glusod 10 mg and 25 mg film-coated tablets, from Medochemie Limited.

The product is indicated for:

- Type 2 diabetes mellitus
  Glusod 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 diabetes
- Heart failure
  Glusod is indicated in adults for the treatment of symptomatic chronic heart failure
  Chronic kidney disease
- Glusod is indicated in adults for the treatment of chronic kidney disease

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Jardiance 10 mg and 25 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/14/930) since 22 May 2014.

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Cyprus, Czechia, Estonia, Greece, Latvia, Lithuania, Malta, Portugal, Romania, Slovakia, Slovenia and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Glusod 10 mg and 25 mg are film-coated tablets. The two strengths of the film-coated tablets can be distinguished by form, size, and debossing and are as follows:

Glusod 10 mg
The 10 mg tablets contain as active substance 10 mg of empagliflozin and are yellow, round, convex, film-coated tablets with a diameter of 6 mm, debossed "E" on one side and plain on the other side.

Glusod 25 mg
The 25 mg tablets contain as active substance 25 mg of empagliflozin and are yellow, oval, convex, film-coated tablets with a diameter of 11,5 mm x 6,2 mm, debossed "MC" on one side and plain on the other side.

The excipients are:
Tablet core: lactose monohydrate; cellulose, microcrystalline (E460); croscarmellose sodium (E468); hydroxypropyl cellulose (E463); silica, colloidal anhydrous (E551) and magnesium stearate (E470b).
Tablet coating: hypromellose; titanium dioxide (E171); macrogol (E1521); talc (E553b) and yellow iron oxide (E172).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in polyvinyl chloride/polyvinylidene dichloride-aluminium (PVC/PVDC-Alu) blisters.

II.2 Drug Substance

The active substance is empagliflozin, an established active substance not described in the European or British Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is practically insoluble in water. For this product, the same polymorphic form is consistently produced. Empagliflozin contains 6 chiral centers.

Two Active Substance Master File (ASMF) procedures are 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.

Manufacturing process

ASM 1

The manufacturing process starts from two starting materials and comprises four chemical transformation steps followed by purification/crystallisation, drying and milling. In the second branch of the synthesis an intermediate is manufactured in one chemical transformation step from the third starting material and is introduced in the third step. No class 1 organic solvents or heavy metal catalysts are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

ASM 2

The manufacturing process starts from the first two starting materials in five chemical transformation steps with three isolated intermediates and two non-isolated intermediates followed by a final purification step. The third starting material is introduced in the third stage of the synthesis after which three chemical transformations take place. No class 1 organic solvents or heavy metal catalysts are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and is based on the specifications by the ASMs. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for four batches (two per ASM).

Stability of drug substance

ASM 1

Stability data on the active substance have been provided for three production scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for two years. Based on the data submitted, a retest period could be granted of two years when stored under the stated conditions.

ASM 2

Stability data on the active substance have been provided for three production scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of 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 drug product was developed to be similar with the reference product. Particle size has been discussed. The

formulation was tested in different studies. The dissolution method is described and the discriminatory capacity of the method was demonstrated.

Manufacturing process

The manufacturing process consists of wet granulation, blending, tableting, film-coating and packaging. The manufacturing process is regarded as a standard process. Process validation data on the product have been presented for three commercial batches of minimum batch size in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation. The manufacturing process has been validated according to relevant European/ICH guidelines.

Control of excipients

The choice of excipients is justified and their functions explained. The excipients comply with Ph.Eur. and USP requirements. 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 appearance, disintegration, identification of active, identification of colorants, dissolution, uniformity of dosage units, assay, related substances and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data on two full scaled batches from one production site has been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three production batches per strength stored at 25°C/60% RH (12 months (1 batch of each strength) and 24 months (2 batches of each strength)) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions needed to be included in the SmPC or on the label.

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

Scientific data and/or certificates of suitability issued by the EDQM for 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 Glusod 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 Glusod is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Jardiance which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Empagliflozin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Glusod 25 mg film-coated tablets (Medochemie Limited, Cyprus) was compared with the pharmacokinetic profile of the reference product Jardiance 25 mg film-coated tablets (Boehringer Ingelheim International GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. Dissolution studies were conducted

in different pH conditions (pH 1, pH 4.5 and pH 6.8) in support of the bioequivalence study and the biowaiver for the 10 mg strength. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements are met for the biowaiver of the 10 mg strength, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. 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),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence study

Design

A pivotal, open-label, single-dose, randomised, two-period, two-sequence, bioequivalence study was carried out under fasted conditions in 32 healthy male (25) and female (7) subjects, aged 18-72 years. Each subject received a single dose (25 mg) of one of the two empagliflozin formulations. The tablet was orally administered with 240 mL of a 20% glucose solution in water after a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days. The subjects received 60 mL of 20% glucose solution in water every 15 minutes after administration until 4 hours after dosing, in both periods. The subjects had free access to water until 1 hour pre-dose and they were not allowed to drink any other liquids until 1 hour post-dose.

Blood samples were collected pre-dose and at 0.083, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Empagliflozin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of empagliflozin. 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
One subject was withdrawn from the study due to personal reasons. 31 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of empagliflozin, 25 mg under fasted conditions.

Treatment N=31	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	2352 ± 533	2475 ± 541	271 ± 61	2.50 (0.75 – 8.00)
Reference	2359 ± 521	2478 ± 528	281 ± 52	2.00 (0.75 – 6.00)
***Ratio (90% CI)**	1.00 (0.97 – 1.02)	-	0.96 (0.91 – 1.01)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**In-transformed values*

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 Glusod is considered bioequivalent with Jardiance.

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 Glusod.

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

Important identified risks	None
Important potential risks	• Urinary tract carcinogenicity • Pancreatitis
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 Jardiance. 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 Jardiance 10 mg and 25 mg film-coated tablets (EMEA/H/C/002677) for key safety messages and Bupalyn (Ibuprofen lysine) 400 mg, film-coated tablets (PT/H/2261/001-002/DC) for design/layout. 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

Glusod 10 mg and 25 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Jardiance 10 mg and 25 mg film-coated tablets. Jardiance 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Glusod with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 February 2024.

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
-	-	-	-	-	-