

Public Assessment Report

Scientific discussion

Axavel

(sitagliptin hydrochloride monohydrate)

SE/H/2128/01-03/DC

This module reflects the scientific discussion for the approval of Axavel. The procedure was finalised on 2021-11-30. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Axavel, 25 mg, 50 mg, 100 mg, film-coated tablet.

The active substance is sitagliptin hydrochloride monohydrate. 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 Axavel, 25 mg, 50 mg and 100 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Genepharma S.A, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and EL as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Januvia, 25 mg, 50 mg and 100 mg, film-coated tablet, authorised in the Union since 2007, with Merck Sharp & Dohme B.V. as marketing authorisation holder.

The reference product used in the bioequivalence study is Januvia, 100 mg, film-coated tablet from Poland with Merck Sharp & Dohme B.V. (NL) 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

Pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin are well known. As sitagliptin 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 Axavel 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 Axavel 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 SITAGLIPTIN FILM COATED TABLETS 100 mg with the reference product Januvia 100 mg film-coated tablets.

Pharmacokinetic properties of the active substance

Plasma AUC of sitagliptin increased in a dose-proportional manner and the pharmacokinetics of sitagliptin is not affected by food.

Study ARL/18/443

Methods

This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Axavel (sitagliptin), 100 mg, film-coated tablets with Januvia®, 100 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72.00 hours post-dose. Plasma concentrations of sitagliptin 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 in 2020.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic/geometric mean $\pm$ SD, $t_{\max}$ median, range) for sitagliptin, n=24.

Treatment	AUC _{0-t} xg*h/ml	C _{max} xg/ml	t _{max} h
Test	4881.17 $\pm$ 642.58	526.6 $\pm$ 147.15	2.000 (1.000 - 5.000)
Reference	4788.87 $\pm$ 722.572	484.52 $\pm$ 92.084	2.500 (1.670 - 6.000)
*Ratio (90% CI)	102.16 (100.13-104.23)	107.18 (98.76 - 116.31)	-
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(s) of 50 and 25 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 strengths of 50 and 25 mg 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 sitagliptin is linear between 1.5 and 800 mg.

Based on the submitted bioequivalence study Axavel, 100 mg, film-coated tablet is considered bioequivalent with reference product Januvia, 100 mg, film-coated tablet and, as stated above, biowaiver of the 25 and 50 mg strength is acceptable.

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 Axavel.

Safety specification

The MAH has submitted the version 0.2 RMP dated 2021-03-08 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Pancreatic cancer
Missing information	• Exposure during pregnancy and lactation

The proposed safety concerns in the RMP for Axavel is in line with that of the reference product.

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 (adverse reactions reporting and signal detection) 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 Safety concerns have been updated with “and lactation” under point Missing information.

The submitted Risk Management Plan, version 0.2 signed 2021-03-08 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

The package leaflet 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 PIL was English.

The results show that the package leaflet 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

The quality of the generic product, Axavel, is found adequate. There are no objections to approval of Axavel 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 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 Axavel, 25 mg, 50 mg, 100 mg, film-coated tablet was positively finalised on 2021-11-30.

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)