LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sitagliptin Laurus
(sitagliptin hydrochloride monohydrate)

SE/H/2164/01-03/DC

This module reflects the scientific discussion for the approval of Sitagliptin Laurus. The procedure was finalised on 2022-03-04. 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 Sitagliptin Laurus, 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 Sitagliptin Laurus, 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, Laurus Generics GmbH, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE and DK as concerned member states (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 tablets authorised in the Union since 2007, with Merck Sharp & Dohme BV as marketing authorisation holder.

The reference product used in the bioequivalence study is Januvia, 100 mg, film-coated tablet from NL with Merck Sharp & Dohme BV 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 Sitagliptin Laurus 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 Sitagliptin Laurus 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 with the reference product Januvia.

Pharmacokinetic properties of the active substance
Absorption: The absolute bioavailability of sitagliptin is approximately 87%. Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median t_{max}) occurring 1 to 4 hours post-dose.

Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Linearity: Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Elimination: The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours.

Study 62020
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Sitagliptin, 100 mg, film-coated tablet with Januvia, 100 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 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 between 28/08/2020 and 10/09/2020.

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 sitagliptin, n=35.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3817.401 ± 627.564**	**344.09 ± 64.786**	**3.00 (1.00-5.52)**
Reference	**3831.205 ± 628.346**	**343.67 ± 66.172**	**3.00 (1.00-6.00)**
***Ratio (90% CI)**	**98.89 (97.34-100.48)**	**98.02 (93.15-103.15)**	**-**

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 strengths of 25 mg and 50 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation was 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) and the Sitagliptin film-coated tablets 25, 50 and 100 mg product-specific bioequivalence guidance (EMA/CHMP/158934/2016). The bioanalytical method was adequately validated.

Absence of studies with the additional strengths of 25 mg and 50 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) are fulfilled and since the pharmacokinetics of sitagliptin is linear.

Based on the submitted bioequivalence study, Sitagliptin Laurus is considered bioequivalent with Januvia.

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 Sitagliptin Laurus.

Safety specification

The MAH has submitted the version 1.0 RMP dated 02.03.2021 and proposed the following summary safety concerns:

Table SVIII.1: Summary of safety concerns

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

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 1.0 signed 02.03.2021 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 (PIL) has been performed on the basis of a bridging report making reference to:

Content
Januvia 25 mg, 50 mg, 100 mg film-coated tablets. The user test of the Januvia leaflet was assessed and accepted in EMEA/H/C/000722.

Layout
Capecitabin Tiefenbacher 500 mg film-coated tablets. The user test of the Capecitabin Tiefenbacher leaflet was assessed and accepted in BE/H/0196/01-02/DC.

The bridging has been assessed and accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Sitagliptin Laurus, is found adequate. There are no objections to approval of Sitagliptin Laurus, 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 Sitagliptin Laurus, 25 mg, 50 mg, 100 mg, Film-coated tablet was positively finalised on 2022-03-04.

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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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