

Public Assessment Report

Scientific discussion

Sitagliptin Jubilant (sitagliptin)

SE/H/2308/01-03/DC

This module reflects the scientific discussion for the approval of Sitagliptin Jubilant. The procedure was finalised at 2024-04-25. For information on changes after this date please refer to the module ‘Steps taken after the finalisation of the initial procedure - Summary’.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Sitagliptin Jubilant, 25 mg, 50 mg, 100 mg, Film-coated tablet.

The active substance is sitagliptin phosphate monohydrate, sitagliptin. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors (ATC code: A10BH01). The improvement in glycaemic control observed with this medicinal product is mediated by enhancing the levels of active incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced, and glucagon secretion is not suppressed.

For adult patients with type 2 diabetes mellitus, Sitagliptin Jubilant is indicated to improve glycaemic control:

as monotherapy:

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with:

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma (PPAR γ) agonist (i.e. a thiazolidinedione) when use of a PPAR γ agonist is appropriate and when diet and exercise plus the PPAR γ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with:

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- a PPAR γ agonist and metformin when use of a PPAR γ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Sitagliptin Jubilant is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.

II.2 General comments on the submitted dossier

The application for Sitagliptin Jubilant, 25 mg, 50 mg, 100 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 DE and ES 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, film-coated tablet authorised in 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 IE with Merck Sharp & Dohme B.V. as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU. An updated QP declaration has been provided, which includes two manufacturers of intermediate(s), Jiangxi Long Life Bio-pharmaceutical Co., Ltd., China and Actis Generics Private Limited, India, which are in accordance with the Certificate of suitability, R0-CEP 2021-175-Rev 00.

GCP aspects:

A statement on the application of appropriate GCP standards in the submitted study has been provided. The clinical and the bioanalytical facilities were inspected by the PT authority (INFARMED) in 2018. The inspectors considered that despite the findings raised during the inspection, the inspected study had been conducted in accordance with the protocol and GCP.

No issues regarding GCP have been identified during the assessment of the bioequivalence study SITA-20-035. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology

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 Jubilant 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 Jubilant from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study comparing Sitagliptin Jubilant (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 SITA-20-035

Methods

This was a single-dose, two-way crossover study conducted in 36 healthy volunteers (36 completed), 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 60 hours post-dose. Plasma concentrations of sitagliptin 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 20/JUN/2022 and 02/AUG/2022.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, t_{max} median, range) for sitagliptin, n=36.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	3479.4 $\pm$ 519.5	380.5 $\pm$ 84.5	3.00 (0.50-6.00)
Reference	3515.4 $\pm$ 551.6	387.9 $\pm$ 88.3	3.00 (0.75-6.00)
*Ratio (90% CI)	99.88 (96.24-101.91)	99.70 (93.34-103.34)	-
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 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 study design was also in accordance with the requirements for bioequivalence demonstration in 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/Corr) are fulfilled and since the pharmacokinetics of sitagliptin is linear over the therapeutic dose range.

Based on the submitted bioequivalence study, Sitagliptin Jubilant 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.

Pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Jubilant.

Safety specification

The MAH has submitted the version 1.0 RMP dated 20 October 2022 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 20 October 2022 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.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date

The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Sitagliptin Jubilant, is found adequate. There are no objections to approval of Sitagliptin Jubilant, 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.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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 PL 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. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-