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Public Assessment Report

Scientific discussion

Sitagliptin IASIS
Sitagliptin

SK/H/0299/001/DC

Date: March 2025

This module reflects the scientific discussion for the approval of Sitagliptin IASIS. The procedure was finalised on 19 January 2024. 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, the Member States have granted a marketing authorisation for Sitagliptin IASIS, oral solution, 25 mg/mL from IASIS PHARMA, Greece.

The product is indicated for adult patients with type 2 diabetes mellitus. It 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 (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ 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 PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Sitagliptin IASIS 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.

A comprehensive description of the indications and posology is given in the SmPC.

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

This marketing authorisation application (MAA) was a duplicate procedure to already authorised dossier submitted under procedural number SK/H/0261/001/DC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as an oral solution containing 25 mg/mL of sitagliptin as active substance. 100 mL oral solution is in an amber (type III) glass bottle inserted into a carton box. The

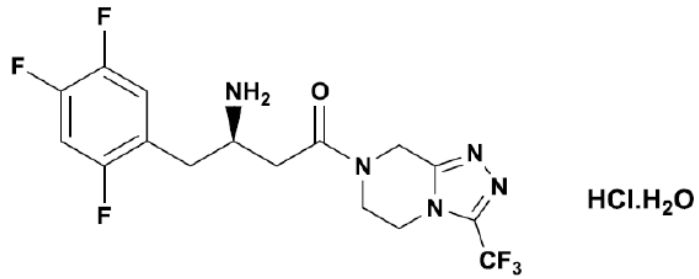
closure of a bottle is sealed with a child-resistant and tamper evident cap with plug. One CE marked (CE 0459) 5 ml oral medication syringe (plastic dosing) with 0.5 ml graduation is co-packed.

The other ingredients are:
sodium methyl parahydroxybenzoate (E219)
hydroxyethylcellulose (E1525)
citric acid (E330)
disodium edetate (E385)
polysorbate 80 (E433)
butylhydroxyanisole (E320)
sodium citrate (E331)
Polisucra 7477 (containing sucralose (E955), acesulfame K (E950) and forest fruits flavor)
forest fruits flavor (consisting of maltodextrin (E1400), modified starch (E1400-E1500), lactic acid (E270), benzyl alcohol (E1519), ethanol (E1510), ethyl butyrate, frambinon crystal, propylene glycol (E1520))
Purified water

II.2 Drug Substance

Sitagliptin hydrochloride monohydrate

Active substance structure:



Empirical formula: $C_{16}H_{15}F_6N_5O \bullet HCl \bullet H_2O$

Chemical name: ((3*R*)-3-Amino-1-(3-(trifluoromethy1)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-y1)-4-(2,4,5-trifluorophenyl)butan-l-one hydrochloride monohydrate

Appearance: White to off-white powder.

Solubility: Soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in n-heptane.

Chirality: Sitagliptin hydrochloride monohydrate has one chiral centre. Drug substance manufactured at production site is consistent "R-isomer".

Manufacturing: Active substance, sitagliptin hydrochloride monohydrate, is not described in Ph.Eur. Active substance master file (ASMF) procedure was followed and approved via a work-sharing procedure for this drug substance.

Specification: The control tests and specifications for drug substance product are adequately drawn up. The specification of the active pharmaceutical ingredient (API) used by the finished product manufacturer follows the specification in place by the active substance manufacturer in the approved ASMF.

Stability: The re-test period of 36 months was justified based on the data provided in the ASMF.

II.3 Medicinal Product

Pharmaceutical development

The main aim of the development was to develop a new oral pharmaceutical form for sitagliptin as a generic to Januvia film-coated tablets. A single strength of the product was developed whereby the required dose can be adjusted by the administered volume.

This was a duplicate application of the same dossier as approved in decentralised procedure SK/H/0261/001/DC. The proposed product, sitagliptin 25 mg/ml oral solution, was originally formulated with sweetener Polisucra 7476. An updated composition was proposed, i.e. sweetener Polisucra 7476 was changed to Polisucra 7477 whereby sodium saccharin was changed for acesulfame K. Updated composition was accepted for both procedures (SK/H/0261/001/DC and SK/H/0299/001/DC).

Manufacturing

The finished product is manufactured by mixing of all components. A detailed description of the process has been provided in the dossier. In brief, it involves mixing of all components in the mixing vessel, pH adjustment, filtration and filling in the proposed container.

Product specification

The finished product release and shelf-life specifications include appropriate tests and limits for appearance (visual), degree of coloration of the liquid (Ph.Eur), clarity and degree of opalescence of liquids (Ph.Eur), pH range (Ph.Eur), relative density (Ph.Eur), uniformity of delivered dosed (Ph.Eur), uniformity of dosage units (Ph.Eur), deliverable volume (USP), container closure integrity (in-house), assay of sitagliptin (in-house, HPLC), related substances (in-house, HPLC), and microbiological quality (Ph. Eur). The proposed specification for the finished product is in line with ICH Q6A.

Stability

Stability data up to 24 months of storage at the long-term conditions (2-8°C) were presented for the composition with Polisucra 7477. The proposed shelf life of 24 months was considered acceptable. Final storage conditions were as follows: Store in a refrigerator (2°C to 8°C). After first opening, store in a refrigerator (2°C to 8°C). In-use stability data was described in detail and supports the shelf life of 90 days (3 months) after first opening.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Quality part of the dossier was adequately presented. Final drug product composition with respect to sweetener was changed in both duplicates and supported with relevant data.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin are well known. As sitagliptin is a widely used, well-known active substance, the applicant has not provided additional

studies, and further studies were not required. Overview based on literature review was, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Applicant submitted consumption data for sitagliptin in kg/year over a period of 4 years (2017-2020) from concerned member states (CZ, SK, HR, RO, UK), which showed descending trend.

Applicant calculated $PEC_{surface\ water}$ which was below 1 and therefore, it was concluded, that further testing in the aquatic compartment is not necessary and that the drug substance and/or its metabolites are unlikely to represent a risk to the aquatic environment. Log Kow was determined experimentally.

III.3 Discussion on the non-clinical aspects

Sufficient references to published non-clinical data were provided for this generic application, which was considered adequate. Presented values of PEC indicated that sitagliptin does not present a risk for the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview on the clinical pharmacology, efficacy and safety was adequate and based on relevant literature.

The current EMA Guideline on the Investigation of Bioequivalence indicates that in cases where the test product is an oral solution which is intended to be bioequivalent to another immediate release oral dosage form, bioequivalence studies are required. The reference medicinal product of the current application is Januvia 100 mg film-coated tablets, therefore, as per the guideline requirements, the applicant has performed a bioequivalence study.

IV.2 Pharmacokinetics

Bioequivalence study

To support the application, the applicant has submitted as a report 1 bioequivalence study investigating strength 50 mg/2 mL of sitagliptin.

A randomised, open-label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of sitagliptin hydrochloride 50 mg/2 mL (at the dose of 100 mg/4 mL) oral solution with Januvia 100 mg film-coated tablets was performed in normal, healthy, adult, human subjects under fasting conditions.

Population(s) studied

There were 24 subjects enrolled in the bioequivalence study (adult males).
23 subjects were included in the pharmacokinetic and statistical analysis of bioequivalence.
All 24 subjects were considered in the safety analysis. Safety of subjects was evaluated through assessment of adverse events, standard laboratory evaluations, vital signs and electrocardiograph.

Analytical methods

The information given by the bioanalytical study report confirmed that the analytical method established was suitable to determine sitagliptin in human plasma and provided accurate, precise and

reproducible results. The acceptance criteria laid down in the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.*) were fulfilled.

Pharmacokinetic variables

The pharmacokinetic parameters of bioequivalence study were C_{max}, AUC_{0-t} (main pharmacokinetic parameters), T_{max}, $AUC_{0-\infty}$, $AUC_{0-t/\infty}$ and T_{half}.

Statistical methods

Pharmacokinetic and statistical analyses were generated using SAS® version 9.4 (GLM procedure). Block randomisation was used to randomize the subjects. The study was open label, but the analysts were kept blinded.

Bioequivalence was concluded if the 90% confidence interval of geometric mean ratio of log transformed pharmacokinetic parameters C_{max} and AUC_{0-t} between test and reference products falls within the range of 80.00% to 125.00% for sitagliptin.

The analysis of variance model included sequences, subject within sequence, period and treatment as fixed factors. A separate ANOVA model was used to analyse each of the parameters.

Results

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product T	Reference Product R
$AUC_{(0-inf)}$ (ng*hr/mL)	5640.715±778.029	5492.439±784.342
$AUC_{(0-t)}$ (ng*hr/mL)	5589.723±777.034	5443.247±785.003
C_{max} (ng /mL)	525.262±91.570	545.828±122.784
t_{max} [1] (hrs)	2.000(1.330-5.000)	2.000(1.000-5.000)

[1] Median (Min, Max)

Pharmacokinetic parameter	Geometric Mean Ratio Test T/Ref R	Confidence Intervals	CV%[1]
$AUC_{(0-inf)}$	102.8464	100.2343-105.5266	5.0685
$AUC_{(0-t)}$	102.8441	100.2204-105.5365	5.0914
C_{max}	97.1958	90.2419-104.6857	14.6944

[1] Estimated from the Residual Mean Squares.
The 90% confidence interval of geometric mean ratio of log transformed pharmacokinetic parameters C_{max} and AUC_{0-t} between test and reference products falls within the range of 80.00 % to 125.00 % for Pirfenidone

AUC_{0-t}	Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max}	Maximum plasma concentration
t_{max}	Time until C_{max} is reached

The 90 % confidence intervals of the ratios are within the acceptance range (0.80–1.25) for the ln transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The results of the study show bioequivalence between test and reference medicinal products when administered under fasting conditions.

Conclusion on bioequivalence study

Based on the submitted bioequivalence study Sitagliptin IASIS oral solution 50 mg/2 mL was considered bioequivalent with Januvia 100 mg film-coated tablets.

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 Sitagliptin IASIS.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	Pancreatic cancer Overdose due to dosing errors*
Missing information	Exposure during pregnancy and lactation

Source: List of safety concerns as per reference medicinal product Januvia.
* IASIS SmPC for sitagliptin 25 mg/mL oral solution

IV.4 Discussion on the clinical aspects

Based on the submitted bioequivalence study sitagliptin 25 mg/mL oral solution (from IASIS PHARMA, Greece) is considered bioequivalent with Januvia 100 mg film-coated tablets (Merck Sharp & Dohme B.V., the Netherlands).

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

This was an application for a marketing authorisation (MAA) of medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended. Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS. The applicant, PHARMA-DATA Research and Development S.A., Greece has submitted this MAA under procedural number SK/H/0299/001/DC.

Reference medicinal product was Januvia, 100 mg, film-coated tablets from Merck Sharp & Dohme B.V., the Netherlands, authorised in the European Union via centralised procedure (EMEA/H/C/722) since 21 March 2007.

Based on the results of submitted bioequivalence study it was concluded, that Sitagliptin IASIS 25 mg/mL oral solution is bioequivalent with the reference medicinal product Januvia, 100 mg, film-coated tablets.

Quality aspects of the dossier were adequately described; specifications of API sitagliptin were appropriately justified in ASMF and that of finished medicinal product are in line with ICH Q6A.

There was no discussion in the CMDh. Agreement between the member states was reached during a written procedure. Based on submitted data the member states considered that the essential similarity with the reference medicinal product Januvia was adequately demonstrated and have, therefore, granted marketing authorisation. This decentralised procedure was positively concluded on 19 January 2024 (D210).