COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sitagliptine Sandoz 25 mg, 50 mg, and 100 mg film-coated tablets (sitagliptin hydrochloride)

NL/H/4930/001-003/DC

Date: 22 July 2021

This module reflects the scientific discussion for the approval of Sitagliptine Sandoz 25 mg, 50 mg, and 100 mg film-coated tablets. The procedure was finalised at 17 February 2021. 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
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
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 Sitagliptine Sandoz 25 mg, 50 mg, and 100 mg film-coated tablets, from Sandoz B.V.

The product is indicated for adult patients with type 2 diabetes mellitus. Sitagliptin 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 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Januvia 25 mg, 50 mg and 100 mg film-coated tablets which have been registered in the EEA by Merck Sharp & Dohme Ltd, since 20 March 2007 by a centralised procedure (EU/1/07/383).

The concerned member states (CMS) involved in this procedure were
25 mg strength: Austria, Belgium, Denmark, , Finland, Hungary, Iceland, Italy, Norway, Portugal, Spain, Sweden and the United Kingdom

50 mg strength Austria, Belgium, Denmark, Finland, France, Hungary, Iceland, Italy, Norway, Portugal, Spain, Sweden and the United Kingdom
100 mg strength: Austria, Belgium, Czech Republic, Denmark, Finland, France, Hungary, Iceland, Italy, Norway, Portugal, Spain, Sweden and the United Kingdom

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

II. QUALITY ASPECTS

II.1 Introduction

Sitagliptin 25 mg film-coated tablets are pink, round, biconvex film-coated tablets debossed with “ST 25” on one side.
Sitagliptin 50 mg film-coated tablets are light pink, round, biconvex film-coated tablets debossed with “ST 50” on one side.
Sitagliptin 100 mg film-coated tablets are light brown, round, biconvex film-coated tablets debossed with “ST 100” on one side.

The tablets contain as active substance sitagliptin hydrochloride monohydrate equivalent to 25 mg, 50 mg or 100 mg sitagliptin.

The film-coated tablets are packed in Aluminum blisters (OPA/Al/PVC-Al) or in transparent PVDC blisters (PVC/PE/PVDC-Al).

The excipients are:
Tablet core - calcium hydrogen phosphate (E341), microcrystalline cellulose (E460), croscarmellose sodium (E468), sodium stearyl fumarate and magnesium stearate (E470b).
Film-coating - hypromellose (E464), hydroxypropylcellulose (E463), macrogol (E1521), titanium dioxide (E171), yellow iron oxide (E172) red iron oxide (E172), black iron oxide, (E172) (only applicable for the 100 mg strength), talc (E553b)

The three tablet strengths are fully dose proportional with respect to the tablet core.

II.2 Drug Substance

The active substance is sitagliptin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance sitagliptin hydrochloride is a white to off-white crystalline powder. It is soluble in water, N,N-Dimethylformamide, slightly soluble in methanol, very slightly soluble in 2-propanol and insoluble in cyclohexane. It has one chiral centre in its structure. Based on the chemistry there is a possibility of 2 stereo isomers i.e., R-Isomer and S-Isomer. The active substance is the R-Isomer. The substance is slightly hygroscopic. The manufacturing process produces sitagliptin hydrochloride crystalline form-III.

The Active Substance Master File (ASMF) procedure is 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

The manufacturing process consists of three stages. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The MAH has adopted the tests and limits as proposed by the ASMF-holder, however there are some differences (slightly different limit for the chloride content and no test for heavy metals) which are acceptable. Drug substance specifications are applied for description, identification , water content, sulphated ash, chloride content (potentiometric titration), related substances, enantiomeric purity, assay, and residual solvents .. Sufficient information on the validation/verification of the (in-house) test methods has been provided. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance has been provided for nine batches (three batches per strength) stored at 40°C/75% RH (6 months) and 25°C/60% RH (18 months). The proposed retest period of 24 months for the active drug substance, without special storage conditions, is justified as no clear trends or significant changes were observed for any of the tested parameters.

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 choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified. The composition of the biobatch used in the bioequivalence studies was similar to the proposed marketed product. For the two lower strengths a biowaiver of strength is requested. In support of the biowaiver of strengths comparative dissolution studies was performed. The presented data confirms the adequacy of waiving additional *in vivo* bioequivalence testing and biowaiver of strengths is considered acceptable from the chemical-pharmaceutical point of view. The dissolution method used for dissolution testing of registration batches was shown to be discriminatory.

Manufacturing process

The product is manufactured using a roller compaction technique to improve tablet blend flowability. The conventional manufacturing techniques are applied. The process is classified as a standard process.. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph. Eur. requirements except for the iron oxides. The three iron oxides (yellow, red, black) are in compliance with Commission Regulation EU 231/2012. 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, identification and assay of the active substance, water activity, uniformity of dosage units, degradation products, disintegration and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scale batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The stability study under long term and accelerated conditions demonstrate that the product in both chosen packaging materials is stable during the tested period. The photostability study has been performed in line with ICH Q1B. On basis of the data submitted, a shelf life was granted of 24 months for both packings (transparent PVC/PE/PVDC blister, Al-Al blister). This medicinal product does not require any special storage condition.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sitagliptine Sandoz 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 Sitagliptine Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

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

Sitagliptin hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sitagliptine Sandoz 100 mg film-coated tablets (Sandoz B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Januvia 100 mg film-coated tablets (Merck Sharp & Dohme Ltd, The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver was requested for the 25 mg and 50 mg strengths. In support of the biowaiver of strengths comparative dissolution studies were performed. The presented data confirms the adequacy of waiving additional *in vivo* bioequivalence testing and biowaiver of strengths is considered acceptable from the chemical-pharmaceutical point of view.

Bioequivalence study

Design

A single-centre, randomised, single-dose, open-label, three-period, six-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male/female subjects, aged 22 - 67 years. Each subject received one dose (100 mg) of one of the 2 sitagliptin hydrochloride formulations. The tablet was orally administered with water after fasting. There were three dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0, 16.0, 24.0, 36.0, 48.0, and 72.0 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the tablet can be taken with or without food. As such, the fasting conditions applied in the study are acceptable.

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
A total of 36 subjects were enrolled in the bioequivalence study of which 30 subjects were randomised and received at least one dose of study medication. A total of 27 subjects completed the study and of these subjects N=27 were included in pharmacokinetic – and statistical analysis for A/B comparison (EU reference) and 29 for A/C comparison (Australian reference).
One subject has been withdrawn due to non-compliance (unscheduled concomitant medication). Two subjects had incomplete participation. These subjects were withdrawn from Period 2 due to usage of concomitant medication and failed attendance, respectively.

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

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	3560.94 (±620.54)	3596.62 (± 631.73)	392.71 (± 96.64)	2.99 (0.74-4.99
Reference	3525.92 (± 698.54)	3563.97 (± 3563.97 712.05)	389.06 (± 101.12)	2.488 (0.99- 6.02)
***Ratio (90% CI)**	1.02 (1.00 – 1.04)	1.02 (1.00-1.04)	1.02 (0.94 – 1.11)	-
Intrasubject CV %	4.17	4.13	17.44	-
Intersubject CV %	16.98	17.08	20.47	-
AUC_{0-t}	Area under the plasma concentration curve from administration to last observed concentration at time t.			
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time.			
C_{max}	Maximum plasma concentration			
t_{max}	Time until Cmax is reached			

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Sitagliptine Sandoz 100 mg is considered bioequivalent with Januvia.

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 Sitagliptine Sandoz.

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

Important identified risks	None
Important potential risks	– Pancreatic cancer
Missing information	– Exposure during pregnancy and lactation

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 Januvia. No new clinical studies were conducted. 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

The MAH provided a bridging report for the user testing. Bridging was performed with product Sitaplis 25, 50 and 100 mg film-coated tablets via procedure DE/H/4682/001-003/DC, approved in 2018. The key safety messages are identical for both products. The lay-out and design is bridged with Rosuvastatin Sandoz 5, 10, 20 and 40 mg film-coated tablets via procedure PT/H/0247-0249/001-004/DC, approved in 2009. Both bridging reports are accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sitagliptine Sandoz 25 mg, 50 mg, and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Januvia 25 mg, 50 mg and 100 mg film-

coated tablets. Januvia 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 Sitagliptine Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 February 2021.

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