COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5271/001-003/DC

31 May 2022

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 9 February 2022. 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 to improve glycaemic control:

<u>as monotherapy:</u>

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

<u>as dual oral therapy in combination with:</u>

- 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.

<u>as triple oral therapy in combination with:</u>

- 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.

Sitagliptine Sandoz 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 product Januvia 100 mg film-coated tablets (sitagliptin phosphate monohydrate) which has been registered through a centralised procedure (EU/1/07/383) in the EEA by Merck Sharp & Dohme B.V. since March 2007 (original product).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech republic (only the 003 strength), Estonia, Finland, France (only the 002 and 003 strengths), Greece, Hungary, Latvia, Lithuania, Malta, Norway, Portugal, Spain and Slovakia (only the 002 and 003 strengths).

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

II. QUALITY ASPECTS

II.1 Introduction

Sitagliptine Sandoz 25 mg film-coated tablets:
Round, pink film-coated tablet with engraved "25" on one side.

Sitagliptine Sandoz 50 mg film-coated tablets:
Round, light beige, film-coated tablet with engraved "50" on one side.

Sitagliptine Sandoz 100 mg film-coated tablets:
Round, beige, film-coated tablet with engraved "100" on one side.

And contains as active substance sitagliptin hydrochloride monohydrate, equivalent to 25 mg, 50 mg or 100 mg of sitagliptin respectively.

The film-coated tablets are packed in opaque PVC/PE/PVDC - Aluminum or OPA/Alu/PVC-Aluminium blisters.

The excipients are:

Tablet core – cellulose – microcrystalline (E460), calcium hydrogen phosphate (E341(ii)), sodium starch glycolate and magnesium stearate (E470b).

Film coating – poly (vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide yellow (E172), iron oxide red (E172) and (only for 50 mg strength) iron oxide black (E172).

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is sitagliptin hydrochloride monohydrate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The European Pharmacopoeia contains a monograph for a different salt of sitagliptin, namely sitagliptin phosphate. Sitagliptin hydrochloride monohydrate is a white or almost white, crystalline powder, soluble in water, sparingly soluble in ethanol and practically insoluble in n-hexane. It has one chiral centre. The R-enantiomer is the active form and used. The obtained polymorphic form is the same crystalline phase in all three validation batches, so the

reproducibility of the manufacturing process for sitagliptin hydrochloride monohydrate in terms of polymorphism has been demonstrated.

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 chemical synthesis comprises seven steps. The process has been described in sufficient detail. The starting materials are acceptable. Bath sizes and yields have been indicated. The carry-over of impurities and control of (potential) genotoxic impurities has adequately been discussed.

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. and in house methods. The batches comply with the proposed specification. The risk assessment regarding elemental impurities demonstrated that the levels of all elemental impurities to be tested for oral products and the intentionally added Rh are below 30% of the ICH Q3D limit. Consequently, no controls for specific elemental impurities are needed. The absence of an additional specification for polymorphism was justified. An additional specification for particle size has been included. 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 three batches stored for 48 months at long term conditions and six months at accelerated conditions in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of 60 months with no special storage conditions required.

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 in relation to the innovator product. The manufacture and composition of the biobatch used in the pivotal bioequivalence study was similar to the proposed marketed product. The dissolution method used for routine dissolution was shown to be discriminatory

and is acceptable. The proposed limit for particle size of the active substance in the drug product is considered justified.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Concerning batch release the MAH has confirmed that the final batch release is carried out in accordance with the relevant EU GMP Guidelines and not merely as an in-process control. Process validation data on the product have been presented for three batches of the 25 mg, 50 mg and 100 mg tablets of each manufacturing site in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph. Eur. requirements. For the ready-to-use mixture (coating agent) in-house specifications are defined. Some additional data, in particular on functionality related characteristics are included. 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, dimensions, water content, disintegration, average weight, uniformity of dosage units (content uniformity), dissolution, related substances, identification of the colourants and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The full risk evaluation on presence of nitrosamine impurities can be accepted.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from six production scale batches of each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scale batches of each tablet strength stored for eighteen months of real-time (25°C/60% RH) and six months accelerated (40°C/75% RH) in accordance with applicable European guidelines demonstrating the stability of the product for 30 months. Photostability studies were performed in accordance with ICH Q1B On basis of the data submitted, a shelf life was granted of 30 months with no special storage conditions required.

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

Sitagliptine hydrochloride monohydrate 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 and one pilot study which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sitagliptin 100 mg film-coated tablets (PharOs., Ltd., Malta) is compared with the pharmacokinetic profile of the reference product Januvia 100 mg film-coated tablets (MSD, the Netherlands). Furthermore, a pilot bioequivalence study was submitted where the pharmacokinetic profiles of two batches of the test product Sitagliptin 100 mg film-coated tablets (PharOs., Ltd., Malta) are compared to the pharmacokinetic profile of the reference product Januvia 100 mg film-coated tablets (MSD, the Netherlands).

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

The designs of the studies 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.

Biowaiver
A bioequivalence study on the highest strength (100 mg strength) has been carried out. Pharmacokinetics are linear in the therapeutic dose range. A biowaiver is requested for the 25 and 50 mg strength as all the following criteria are fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process;
b) the qualitative composition of the different strengths is the same;
c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths;
d) in vitro dissolution data between the 25, 50 and 100 mg (biobatch) showing comparable dissolution have been submitted.

As all these criteria have been fulfilled, the biowaiver is adequate and therefore accepted.

Bioequivalence studies

Study 1
Design
An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-42 years. Each subject received a single dose (100 mg) of one of the two sitagliptin hydrochloride monohydrate formulations. The tablet was orally administered

with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of five days.

Blood samples were collected at pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

Sitagliptine hydrochloride monohydrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sitagliptine hydrochloride monohydrate. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Results
All 40 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=40	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	4800 ± 980	4902 ± 990	586 ± 155	2.14 (0.67 – 5.50)	9.4 ± 2.2
Reference	4928 ± 1118	5031 ± 1133	604 ± 197	2.38 (1.0 – 5.0)	9.1 ± 1.4
***Ratio (90% CI)**	0.98 (0.96 – 1.00)	--	0.98 (0.91 – 1.06)	--	--
CV (%)	6.2	--	19.3	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation
CI confidence interval
**ln-transformed values*

Study 2 (pilot study)
Design
An open-label, balanced, randomized, single-dose, three-treatment, three-sequence, three-period, crossover bioequivalence study was carried out under fasted conditions in 15 healthy male subjects, aged 19-42 years. Each subject received a single dose (100 mg) of one of the three sitagliptin hydrochloride monohydrate formulations in each period. The tablet was

orally administered with 240 ml water after an overnight fast. There were three dosing periods, separated by two washout periods of at least seven days.

Blood samples were collected at pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

Results
Out of a total 15, 12 subjects were eligible for pharmacokinetic analysis. Three subjects did not report to the facility and were withdrawn from the study.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptine hydrochloride monohydrate under fasted conditions. (test 1 VS reference)

Treatment N=12	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	$AUC_{extrapol}$ (%)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)	K_{el} (hr-1)
Test 1	4997.6030 ± 719.55650	5088.1053 ± 716.98374	1.818 ± 0.8749	606.2900 ± 142.50610	2.736 ± 1.2562	8.6452 ± 1.16088	0.0815 ± 0.01109
Reference	4888.9530 ± 788.37980	4981.9618 ± 789.25331	1.905 ± 0.9765	700.1990 ± 287.02420	2.769 ± 1.3786	8.8102 ± 1.28845	0.0802 ± 0.01139
Test 1 (GLSM)	4946.7123	--	--	597.0729	--	--	--
Reference (GLSM)	4817.0897	--	--	643.5982	--	--	--
***Ratio (90% CI)**	102.69 (100.39 – 105.05)	--	--	92.77 (81.26 – 105.91)	--	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
GLSM geometric least squares mean
CI confidence interval

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptine hydrochloride monohydrate under fasted conditions. (test 2 VS reference)

Treatment N=12	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	$AUC_{extrapol}$ (%)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)	K_{el} (hr-1)
Test 2	4850.4890 ± 629.46100	4949.0048 ± 632.58257	2.012 ± 0.9306	622.8930 ± 248.71610	2.356 ± 1.2099	9.0494 ± 1.12660	0.0777 ± 0.00967
Reference	4888.9530 ± 788.37980	4981.9618 ± 789.25331	1.905 ± 0.9765	700.1990 ± 287.02420	2.769 ± 1.3786	8.8102 ± 1.28845	0.0802 ± 0.01139
Test 2 (GLSM)	4885.5964	--	--	606.2617	--	--	--
Reference (GLSM)	4817.0897	--	--	643.5982	--	--	--
***Ratio (90% CI)**	101.42 (99.07 – 103.83)	--	--	94.20 (82.51 – 107.54)	--	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
GLSM geometric least squares mean
CI confidence interval

Conclusion on bioequivalence studies:
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 studies Sitagliptine Sandoz 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 4. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Januvia 100 mg film-coated tablets (EMEA/H/C/000944) for key safety messages and Etoricoxib 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets (EL/H/0198/001-004) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

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 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 concerned 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 9 February 2022.

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