COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sitagliptine/Metformine HCl Sandoz 50/850 mg and 50/1000 mg, film-coated tablets

(sitagliptin hydrochloride monohydrate/ metformin hydrochloride)

NL/H/5234/001-002/DC

Date: 9 November 2021

This module reflects the scientific discussion for the approval of Sitagliptine/Metformine HCl Sandoz 50/850 mg and 50/1000 mg, film-coated tablets. The procedure was finalised on 8 January 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/Metformine HCl Sandoz 50/850 mg and 50/1000 mg, film-coated tablets from Sandoz B.V.

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

- Sitagliptine/Metformine HCl Sandoz is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

- Sitagliptine/Metformine HCl Sandoz is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

- Sitagliptine/Metformine HCl Sandoz is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

- Sitagliptine/Metformine HCl Sandoz is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone 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 Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (EU/1/08/455) marketed by Merck Sharp & Dohme B.V, which has been authorised in the European Union via the centralised procedure since 16 July 2008.

The concerned member state (CMS) involved in this procedure was Austria.

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

II. QUALITY ASPECTS

II.1 Introduction

- Sitagliptine/Metformine HCl Sandoz 50 mg/850 mg is a light orange film-coated tablet of oval, biconvex shape, debossed with “SM 2” on one side. Each film-coated tablet contains sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin, and 850 mg of metformin hydrochloride.
- Sitagliptine/Metformine HCl Sandoz 50 mg/1000 mg is a light red film-coated tablet of oval, biconvex shape, debossed with “SM 3” on one side. Each film-coated tablet contains sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin, and 1000 mg of metformin hydrochloride.

The film-coated tablets are packed in OPA/Aluminium/PVC//Aluminium blisters or PVC/PE/PVDC//Aluminium transparent blisters

The excipients are:
Tablet core – povidone (E1201), sodium laurilsulfate, microcrystalline (E460), croscarmellose sodium (E468) and sodium stearyl fumarate.
Film coating – hypromellose (E464), hydroxypropyl cellulose (E463), triethyl citrate (E1505), titanium dioxide (E171), talc (E553b), yellow iron oxide (E172) and red iron oxide (E172).

II.2 Drug Substances

Sitagliptin hydrochloride monohydrate
The active substance sitagliptin hydrochloride monohydrate is an established active substance not described in the European Pharmacopoeia (Ph.Eur.), but a monograph is available for sitagliptin phosphate monohydrate. Sitagliptin hydrochloride is a white to off-white powder. The drug substance is freely 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. The substance is slightly hygroscopic. The manufacturer consistently produces polymorph 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. The proposed starting materials are considered acceptable and adequate specifications are applied. The manufacturing process has been adequately described.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. 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, related substances, enantiomeric purity, assay, and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Retest period by drug product manufacturer is set in accordance the retest period of the drug substance manufacturer.

Metformin hydrochloride

The active substance metformin hydrochloride is an established active substance described in the Ph.Eur. It appears as white or almost white crystals. Metformin hydrochloride is freely soluble in water, slightly soluble in ethanol, and practically insoluble in acetone and methylene chloride. Polymorphic form II is used.

The CEP procedure is used for metformin hydrochloride. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification comprises the tests and limits of the Ph.Eur. monograph, the CEP with additional requirements for residual solvents and particle size. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 choice of the manufacturing process, wet granulation, is adequately justified also in relation to the innovator product.
Bioequivalence studies for both strengths have been performed. In support of the bioequivalence study the MAH performed comparative *in vitro* dissolution studies at different dissolution media. The qualitative composition of the product for registration and the reference product are not exactly the same. The generic product differs in the drug substance salt type. The generic formulation contains Sitagliptin as a hydrochloride monohydrate salt, whereas the reference product contains Sitagliptin as a phosphate monohydrate salt. The other differences concern the film former and pigment (non-functional coating is involved). This is acceptable. Overall, the pharmaceutical development has been adequality performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. Standard manufacturing techniques are applied and the manufacturing process can be considered as a standard manufacturing process. Process validation data on the product have been presented for three production scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph. Eur. requirements except the iron oxides. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification and assay of the active substance, water activity, uniformity of dosage units (content uniformity), degradation products, disintegration and microbiological quality. Adequate descriptions and validations of the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided for three full-scale batches of each strength, demonstrating compliance with the release specification. No risk for nitrosamine formation in the drug product was identified.

Stability of drug product
Stability data on the products have been provided for three full-scale batches 25°C/60% RH (18 months), 30°C/60% RH (12 months) and 40°C/75% RH (6 months). There were no significant changes observed at any of the stability testing condition. All stability parameters

remained well within the specification limits. Based on all available stability results the proposed shelf-life of 2 years for both packaging configurations can be accepted. This medicinal product does not require any special storage condition. The drug product appears to be not light sensitive.

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/Metformine HCl Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sitagliptine/Metformine HCl 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 Janumet, 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 monohydrate and metformin hydrochloride are well-known active substances 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 submitted two bioequivalence studies which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profiles of the test products Sitagliptine/Metformine HCl Sandoz 50 mg/850 mg and 50 mg/1000 mg (Sandoz B.V., NL) were compared with the pharmacokinetic profiles of the reference products Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (Merck Sharp & Dohme B.V, NL).

The choice of the reference product in the bioequivalence studies is justified, as it has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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.

Bioequivalence studies
Bioequivalence study I - 50 mg/1000 mg strength
Design
A single-dose, randomised, three-way, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 20-72 years. Each subject received a single dose (50 mg/1000 mg) of one of the three sitagliptin/metformin formulations. The tablet was administered after the start of high-fat high-calorie breakfast (consisting of two eggs fried in butter, two slices of toast with butter, two strips of bacon, approximately 120 g of hash brown potatoes, and 200 ml of whole milk). There were three dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours for sitagliptin and at 0.5, 1, 1.5, 2, 2.5, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, and 48 hours for metformin after administration of the products.

This design is acceptable. It is a standard crossover study, as described in the guideline. Washout between periods is long enough and sampling schemes are adequate. The provided meal is in accordance with the requirements as per guideline (high-fat, high-caloric meal, between 800 to 1000 calories and approximately 50% of total caloric content of the meal derived from fat).

Results

One subject was withdrawn due to an adverse event (pre-syncope) prior to drug administration. Therefore, a total of 35 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=35	AUC_{0-t} (ug.h/ml)	$AUC_{0-\infty}$ (ug.h/ml)	C_{max} (ug/ml)	t_{max} (h)
Test	14.3 ± 3.68	14.6 ± 3.75	1.59 ± 3.22	4.48 (1.00 - 5.99)
Reference	14.4 ± 4.20	14.7 ± 4.29	1.63 ± 3.66	4.00 (1.49 - 7.98)
***Ratio (90% CI)**	1.00 (0.96-1.04)	1.00 (0.96 -1.03)	0.98 (0.94-1.02)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin under fed conditions.

Treatment N=33	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	1774 ± 317	1804 ± 327	178 ± 42.6	2.50 (0.99 - 5.99)
Reference	1791 ± 354	1822 ± 367	180 ± 48.9	2.49 (0.74 - 5.10)
***Ratio (90% CI)**	0.99 (0.98-1.01)	0.99 (0.98 – 1.01)	1.00 (0.96 -1.04)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Bioequivalence study II - 50 mg/850 mg strength

Design

A single-dose, randomised, open-label, two-way crossover bioequivalence study was carried out under fed conditions in 30 healthy male subjects, aged 19-73 years. Each subject received a single dose (50 mg/850 mg) of one of the 3 sitagliptin/metformin formulations. The tablet was administered after the start of high-fat high-calorie breakfast (consisting of two eggs fried in butter, two slices of toast with butter, two strips of bacon, approximately

120 g of hash brown potatoes, and 200 ml of whole milk. There were three dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours for sitagliptin and at 0.5, 1, 1.5, 2, 2.5, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, and 48 hours for metformin after administration of the products

This design is acceptable. It is a standard crossover study, as described in the guideline. Washout between periods is long enough and sampling schemes are adequate. The provided meal is in accordance with the requirements as per guideline (high-fat, high-caloric meal, between 800 to 1000 calories and approximately 50% of total caloric content of the meal derived from fat).

Results
One subject was withdrawn due to an adverse event (diarrhea) prior to drug administration. Therefore, a total of 29 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin under fed conditions.

Treatment N=29	AUC_{0-t} (ug.h/ml)	$AUC_{0-\infty}$ (ug.h/ml)	C_{max} (ug/ml)	t_{max} (h)
Test	13.09 ± 2.90	13.25 ± 2.93	1.57 ± 0.401	3.99 (0.996 -5.02)
Reference	12.46 ±2.67	12.64 ±2.73	1.45 ± 0.357	4.01 (0.988 -6.02)
***Ratio (90% CI)**	1.05 (1.02-1.08)	1.05 (1.02 -1.08)	1.09 (1.03-1.15)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin under fed conditions.

Treatment N=29	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	1815 ± 321	1846 ± 322	169.0 ± 40.2	2.99 (0.99 - 5.06)
Reference	1761 ± 314	1788 ± 319	159.2 ± 47.7	3.49 (1.00 - 6.01)
***Ratio (90% CI)**	1.03 (1.02-1.04)	1.03 (1.02– 1.05)	1.08 (1.01 -1.15)	--

$AUC_{0-\infty}$	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

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Sitagliptine/ Metformine HCl Sandoz 50 mg/850 mg and 50 mg/1000 mg are considered bioequivalent with Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets.

The MEB has been assured that the bioequivalence studies have 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/Metformine HCl Sandoz.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	- Lactic acidosis
Important potential risks	- Pancreatic cancer
Missing information	- Exposure during pregnancy and lactation

The member states agreed that 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 Janumet. 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 the PL for Janumet (EMEA/H/C/000861) regarding key safety message. The layout is bridged to Rosuvastatin Sandoz (PT/H/0247-0249/001-004/DC). 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/Metformine HCl Sandoz 50/850 mg and 50/1000 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. Janumet 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/Metformine HCl Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 January 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