COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sitaglazamet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (sitagliptin hydrochloride monohydrate & metformin hydrochloride)

NL License RVG: 128975 & 128982

Date: 25 August 2025

This module reflects the scientific discussion for the approval of Sitaglazamet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. The procedure was finalised on 21 February 2023. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Sitaglazamet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets, from Maddox Pharma Swiss B.V.

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

The product 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.

The product 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.

The product 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.

The product 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.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, essential similarity is proven between the new products and the innovator product Janumet 50 mg/850mg and 50 mg/1000 mg film-coated tablets, which has been registered in the EEA since 16 July 2008 via a centralised procedure (EU/1/08/455).

II. QUALITY ASPECTS

II.1 Introduction

Sitaglazamet 50 mg/850 mg is a pink, capsule-shaped, biconvex film-coated tablet approximately 20,2 mm (± 0,2 mm) by 9,9 mm (± 0,2 mm) with "585" debossed on one side and a break-line on the other. The tablet contains as active substance sitagliptin hydrochloride monohydrate equal to 50 mg sitagliptin, and 850 mg metformin hydrochloride.

Sitaglazamet 50 mg/1000 mg is a red, capsule-shaped, biconvex film-coated tablet approximately 21,4 mm (± 0,2 mm) by 10,4 mm (± 0,2 mm) with "5100" debossed on one side and a break-line on the other. The tablets contains as active substance sitagliptin hydrochloride monohydrate equal to 50 mg of sitagliptin and 1000 mg metformin hydrochloride.

The excipients are:
Tablet core - povidone K30 (E1201), sodium lauryl sulphate, microcrystalline cellulose and magnesium stearate.

Film-coat – polyvinyl alcohol (E1203), macrogol (E1521), talc (E553b), titanium dioxide (E171), iron oxide red (E172) and iron oxide black (E172)(50 mg/850 mg only) and iron oxide yellow (E172)(50 mg/1000 mg only).

The two strengths are not dose proportional.

The tablets are packed in polyvinylchloride/polyethylene/polyvinylidene chloride-aluminium (PVC/PE/PVDC-Aluminium) or oriented polyamide/aluminium/polyvinyl chloride-aluminium OPA/Alu/PVC-aluminium, in perforated or non-perforated blisters.

II.2 Drug Substance

The active substances are sitagliptin hydrochloride monohydrate and metformin hydrochloride.

Sitagliptin hydrochloride monohydrate
Sitagliptin hydrochloride monohydrate is not described in the European Pharmacopoeia. The European Pharmacopoeia contains a monograph for a different salt of sitagliptin, namely sitagliptin phosphate. According to art 10(2) of Directive 2001/83/EC (as amended), *"The different salts, esters, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and /or efficacy."* Sitagliptin hydrochloride monohydrate is a white or almost white, crystalline powder, soluble in water; very slightly soluble in ethanol and practically insoluble in hexane. It has one chiral center. The R-enantiomer is the active form and used. The polymorphic form is consistently produced and adequately controlled.

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 seven steps, including a chloride-salt forming step. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements for microbiological quality. 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 from each supplier in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months. Based on the data submitted, a retest period could be granted of 24 months when stored under the stated conditions.

Metformin hydrochloride

The active substance is metformin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Metformin hydrochloride are white or almost white crystals, freely soluble in water, slightly soluble in ethanol (97%), practically insoluble in acetone and in methylene chloride. For this product, polymorphic form I is consistently produced. The different polymorphs may exhibit different aqueous solubility and hence may impact drug release. However, the active substance is classified as a BCS Class III drug exhibiting high solubility and polymorph form I is consistently produced according to XRD and provided data. Hence, further evaluation of the polymorphic form is not deemed necessary.

The CEP procedure is used for the active substance. 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. Two CEPs were provided.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

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 CEPs, with an additional requirement for microbial quality. The absence of additional specifications for polymorphism is justified. Batch analytical data demonstrating compliance with this specification have been provided for twelve batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEPs (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. Optimisation of the manufacturing process has been performed. Adequate justification is provided for the developed QC dissolution test method. Dissolution specifications set are in line with the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017). The products used in the bioequivalence study are acceptable. The omission of a specification for the desired crystalline form of the active substances is adequately justified.

Manufacturing process
The product is manufactured using conventional wet-granulation manufacturing techniques. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full-scale batches per strength per site in accordance with the relevant European guidelines.

Control of excipients
For the Opadry mixtures in-house specifications are defined. The other excipients comply with the Ph. Eur. requirements. Where relevant, additional specifications are set for functionality related characteristics. All 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 both active substance, water content, average mass, dissolution, uniformity of dosage units (content uniformity for sitagliptin and mass variation for metformin), related substances, nitrosamine impurity, 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. Appropriate tests for nitrosamine presence are performed on the final product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches per strength per site 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 full-scale batches per strength per site stored at 25°C/ 60% RH (24 or 12 months), 30°C/ 65% RH (12 months) and at 40°C/75% RH (12 months). The stability was tested in accordance with applicable ICH guidelines demonstrating the stability of the product for 24 months. Photostability data provided are in line with ICH Q1B. The product can be considered as photostable as no adverse observations are noted. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are 'Do not store above 25°C'.

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 MEB considers that Sitaglazamet 50 mg/850 mg and 50 mg/1000 mg have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sitaglazamet 50 mg/850 mg and 50 mg/1000 mg are 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sitagliptin and metformin are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The MEB agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products Sitagliptin/Metformin Hydrochloride 50/850 mg and 50/1000 mg film-coated tablets (Rontis Hellas, S.A., Greece) was compared with the pharmacokinetic profile of the reference products Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (Merck Sharp & Dohme B.V., Netherlands).

The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution study results (with dissolution media 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer) and composition. The formula and preparation of the bioequivalence batches was identical to the formula proposed for marketing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Study 1: single dose Sitagliptin/Metformin Hydrochloride 50/850 mg tablet, fed study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open-label, balanced bioequivalence study was carried out under fed conditions in 34 healthy male subjects, aged 20-39 years. Each subject received a single dose (50/850 mg) of one of the two sitagliptin/metformin formulations. The tablet was orally administered with 240 mL water, 30 minutes after the start of a high fat, high caloric breakfast (946 kcal, 62g carbohydrates, 60g fat, 40g protein). There were two dosing periods, separated by a washout period of 8 days.

Blood samples were collected 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, 3.75, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

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
34 subjects enrolled in the study. All subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin, 50 mg under fed conditions.

Treatment N=34	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	2190 ± 290	2268 ± 301	169 ± 29	4.25 (1.0 – 5.5)
Reference	2158 ± 291	2242 ± 299	164 ± 31	4.5 (1.0 – 6.0)
***Ratio (90% CI)**	1.02 (0.99 – 1.04)	-	1.03 (0.99 – 1.08)	-

$AUC_{0-\infty}$	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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin, 850 mg under fed conditions.

Treatment N=34	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	13929 ± 3162	14189 ± 3118	1504 ± 316	4.5 (1.0 – 8.0)
Reference	14475 ± 3174	14719 ± 3128	1527 ± 316	4.5 (1.0 – 8.0)
***Ratio (90% CI)**	0.96 (0.92 – 1.00)	-	0.99 (0.95 – 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= 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2: single dose Sitagliptin/Metformin Hydrochloride 50/1000 mg tablet, fed study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open-label, balanced bioequivalence study was carried out under fed conditions in 34 healthy male subjects, aged 21-43 years. Each subject received a single dose (50/1000 mg) of one of the two sitagliptin/metformin formulations. The tablet was orally administered with 240 mL water, 30 minutes after the start of a high fat, high caloric breakfast (946 kcal, 62g carbohydrates, 60g fat, 40g protein). There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected 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, 3.75, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is 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

34 subjects enrolled in the study. All subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin, 50 mg under fed conditions.

Treatment N=34	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	2249 ± 328	2324 ± 348	193 ± 40	4.125 (1.25 – 6.0)
Reference	2181 ± 330	2251 ± 347	185 ± 36	3.75 (1.25 – 7.0)
***Ratio (90% CI)**	1.03 (1.01 – 1.05)	-	1.05 (0.99 – 1.11)	-

$AUC_{0-\infty}$	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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin, 1000 mg under fed conditions.

Treatment N=34	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	17045 ± 3609	17254 ± 3593	1900 ± 450	4.5 (1.0 – 6.0)
Reference	16627 ± 3471	16839 v 3724	1854 ± 479	4.5 (1.0 – 6.0)
***Ratio (90% CI)**	0.96 (0.92 – 1.00)	-	0.99 (0.95 – 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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for both products are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Sitaglazamet 50 mg/850 mg and 50 mg/1000 mg are considered bioequivalent with Janumet, 50 mg/850 mg and 50 mg/1000 mg.

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 (RMO), 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 Sitaglazamet 50 mg/850 mg and 50 mg/1000 mg. At the time of approval the most recent version of the RMP was version 1.0 signed 21 February 2022.

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 MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. The MAH has proposed a specific adverse reaction targeted follow-up questionnaire for the safety concerns lactic acidosis for the purpose of collection and reporting of safety 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. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of those products is similar to the pharmacokinetic profile of these reference products. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

The package leaflet (PL) 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 Dutch. The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Sitaglazamet 50 mg/850 mg and 50 mg/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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sitaglazamet 50 mg/850 mg and 50 mg/1000 mg with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 21 February 2023.

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
Type IAin: B.II.b.2.c.1	Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a manufacturer responsible for importation and/or batch release ○ Not including batch control/testing	Yes	04-04-2023	Approved	N/A
Art.61(3)	Add English translations of PIL and labelling to the product information of the above products in order to have bilingual packaging texts	Yes	31-05-2023	Approved	N/A
Type IB: B.II.d.2.d	Change in test procedure for the finished product • Other changes to a test procedure (including replacement or addition)	No	14-06-2023	Approved	N/A
Type IA: B.I.b.2.a	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance • Minor changes to an approved test procedure	No	26-6-2023	Approved	N/A
Type IA: B.I.c.z Type IA: A.4	Change in container closure system of the active substance • Other variation Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel	No No	20-10-2023	Approved	N/A

	excipient (where specified in the technical dossier)				
Type II: C.I.13:	Addition of a bio-equivalence study • Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	No	06-06-2024	Approved	N/A
Type IB: A.2.b	Change in the (invented) name of the medicinal product • for Nationally Authorised Products	Yes	15-08-2024	Approved	N/A
Type IAin: A.5.a	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) • Manufacturer responsible for batch release	Yes	25-09-2024	Approved	N/A
Type IB: B.II.d.1.g	Change in the specification parameters and/or limits of the finished product • Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue	No	21-10-2024	Approved	N/A
Type IB: C.I.2.a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product • Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	26-11-2024	Approved	N/A
Type IAin: A.5.a	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) Manufacturer responsible for batch release	Yes	06-02-2025	Approved	N/A

Type IAin: A.1 Type IAin: C.I.8.a	Change in the name and/or address of the marketing authorisation holder Introduction of , or changes to, a summary of pharmacovigilance system for medicinal products for human use • Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	Yes No	07-02-2025	Approved	N/A

ANNEX 1 - Addition of a bio-equivalence study - other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority (Type II: C.I.13)

I. INTRODUCTION

Sitagliptine/Metformine HCl 50/850 mg and 50/1000 mg film-coated tablets were initially proven bioequivalent to the EU innovator Janumet 50/850 mg and 50/1000 mg film-coated tablets, respectively, by performing two bioequivalence studies in 2020. However, in 2023, an Article 31 Referral was triggered by AEMPS on the benefit-risk balance of the bioequivalent studies performed at the site involved On 24 March 2024, EMA's human medicines committee (CHMP) confirmed its recommendation to suspend the marketing authorisations of, amongst others, Sitagliptine/Metformine HCl. Thus the bioequivalence studies were repeated at another site.

In this application, a generic status is claimed for Sitagliptine/Metformine HCl film-coated tablets versus the European innovator Janumet® film-coated tablets. To compare the rate and extent of absorption between Sitagliptine/Metformine HCl film-coated tablets and Janumet® film-coated tablets, a bioequivalence study was conducted on the 50/850 and 50/1000 mg strength using as a reference product the European innovator sourced from the Belgium market (the marketing authorisation holder is MSD, The Netherlands).

II. NON-CLINICAL ASSESSMENT

Not applicable.

III. CLINICAL ASSESSMENT

GCP aspects

To support the application, the applicant has submitted as report a single dose pivotal bioequivalence study with the 50/850 mg tablet and a single dose pivotal bioequivalence study with the 50/1000 mg tablet carried out. The study is performed in healthy volunteers.
Quality assurance documents were provided. The study center has been inspected by UKMHRA and the WHO.

III.1 Clinical study reports

To support the application, the applicant has submitted as report a single dose pivotal bioequivalence study with the 50/850 mg tablet and a single dose pivotal bioequivalence study with the 50/1000 mg tablet.

BIOWAIVER
Not applicable.

III.2 Clinical study reports

III.2.1 study I: single dose fed study, 50/850 mg tablet

- **Study design**

This was a single-dose, randomised, crossover comparative bioequivalence study. Thirty-six male healthy subjects, aged 18 – 44 years, were dosed in this study. A standardized high fat and high calorie breakfast which was served to all the subjects at about 30 minutes prior to drug administration. Subjects were instructed to finish the high fat and high calorie breakfast within 30 minutes. No food was allowed for at least 4.00 hours post-dose. Subjects received a single dose (50/850 mg; 1 x 50/850 mg tablet) of the Test and Reference sitagliptin/metformin formulation. The tablets were administered in solid form with 240 ml of 20% glucose solution after an overnight fast. After drug administration to avoid hypoglycemia, subjects were administered 60 ml of 20% glucose solution in drinking water every 30 minutes for up to 4 hours post dose.
The washout period was 12 days.

Further information is listed below:
Title:
An open label, balanced, randomized, two-treatment, two-period, single dose, crossover, oral bioequivalence study of Sitagliptin and Metformin Hydrochloride 50mg/850mg film-coated tablets of Rontis Hellas S.A., Greece, compared to Janumet® (sitagliptin and metformin hydrochloride) film-coated tablets 50mg/850mg of Merck Sharp & Dohme B.V., The Netherlands, in healthy, adult, human volunteers under fed conditions.

Blood samples were taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.33, 4.67, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

- Test and reference products

Sitagliptin/Metformin 50/850 tablets have been compared to Janumet 50/850 mg tablets.

Population(s) studied
Thirty-six healthy male subjects, aged 18 – 44 years, were dosed in Period I of this study.
One subjects did not check in for Period 2.
35 subjects completed the study and were included in the analysis.

- Analytical methods

Sitagliptin:
Plasma samples (K2EDTA) were analysed for sitagliptin (together with metformin) using LC-MS/MS. The method was validated (K2EDTA) and a validation report has been provided.
The calibration curve for sitagliptin ranged from about 3 – 1502 ng/ml. A weighted (1/C2) linear regression was performed to determine the concentration of the analyte. Within-run and between-run accuracy and precision were tested on sitagliptin QC sample concentrations of about 3.0, 8.7, 94,

188, 526 and 1141 ng/ml during validation and at about 8.7, 94, 188, 526 and 1140 ng/ml during subject sample analysis.

Selectivity was demonstrated in processed blank plasma samples from 8 different sources, including 1 haemolysed sample and 1 lipemic sample. No endogenous interference was observed with the analytical peak or with that of the internal standard (sitagliptin-d4).
No interference was observed with metformin, metformin-d6, diclofenac, paracetamol, nicotine, caffeine, ondansetron and ranitidine.

Accuracy and precision obtained during validation is shown below:

Between-run precision:	1.7 – 7.2%
Between-run accuracy:	97.2 – 103.1%
Within-run precision:	0.2 – 13.1%
Within-run accuracy:	93.9 – 107.6%

Dilution of samples by a factor 3 and 5 did not affect the accuracy and precision.
No matrix effect (IS-normalised) is observed.
No carry-over is observed.

The stability results, i.e. blood (2h at room temperature), long term stability (134 days at -20°C and -70°C), short term stability (18h30min at room temperature), autosampler stability (119 at 5°C), 5 freeze/thaw cycles stability, and stock solution stability, showed that the analyte is stable under these conditions.

Accuracy and precision obtained during analysis of subjects samples is shown below.

Between-run precision:	2.3 – 3.7%
Between-run accuracy:	99.2 – 100.6%

Plasma samples were stored at -20ºC for 32 days.

5 subject samples had to be reanalysed, due to internal standard response variation.

Incurred sample reanalysis on 156 samples showed good reproducibility (n=155 (99.4%) within the criteria).

Analytical chromatograms were included in the dossier. There were no trends in the IS responses.

Metformin:
Plasma samples (K2EDTA) were analysed for metformin (together with sitagliptin) using LC-MS/MS. The method was validated (K2EDTA) and a validation report has been provided.
The calibration curve for sitagliptin ranged from about 10 – 5003 ng/ml. A weighted (1/C2) linear regression was performed to determine the concentration of the analyte. Within-run and between-run accuracy and precision were tested on metformin QC sample concentrations of about 10, 29, 313, 626, 1753 and 3802 ng/ml during validation and at about 29, 313, 625, 1752 and 3800 ng/ml during subject sample analysis.

Selectivity was demonstrated in processed blank plasma samples from 8 different sources, including 1 haemolysed sample and 1 lipemic sample. No endogenous interference was observed with the analytical peak or with that of the internal standard (metformin-d6).
No interference was observed with sitagliptin, sitagliptin-d4, diclofenac, paracetamol, nicotine, caffeine, ondansetron and ranitidine.

Accuracy and precision obtained during validation is shown below:

Between-run precision:	3.5 – 6.4%
Between-run accuracy:	98.7 – 106.0%
Within-run precision:	0.4 – 9.7%
Within-run accuracy:	94.8 – 110.2%

Dilution of samples by a factor 3 and 5 did not affect the accuracy and precision.
No matrix effect (IS-normalised) is observed.
No carry-over is observed.

The stability results, i.e. blood (2h at room temperature), long term stability (134 days at -20°C and -70°C), short term stability (18h30min at room temperature), autosampler stability (119 at 5°C), 5 freeze/thaw cycles stability, and stock solution stability, showed that the analyte is stable under these consitions.

Accuracy and precision obtained during analysis of subjects samples is shown below.

Between-run precision:	3.0 – 4.8%
Between-run accuracy:	98.8 – 101.4%

Plasma samples were stored at -20ºC for 32 days.

4 subject samples had to be reanalysed, due to internal standard response variation.

Incurred sample reanalysis on 156 samples showed good reproducibility (n=155 (99.4%) within the criteria).

Analytical chromatograms were included in the dossier. There were no trends in the IS responses.

- Pharmacokinetic Variables

Sitagliptin and metformin AUC was calculated by the linear trapezoidal method. C_{max} and t_{max} were derived directly from concentration-time-curve. Elimination rate constant was estimated from the slope of the regression line using the terminal data points of the semi-logarithmic plasma concentration - time curve. $T_{½}$ was calculated as $0.693/k_{el}$.

- Statistical methods

The 90% confidence intervals for the ratio of Test formulation over the Reference formulation were calculated for ln-transformed C_{max} and $AUC_{(0-t)}$ by ANOVA using SAS. Treatment, period, sequence and subjects within sequence were included as effects in the analysis.

Bioequivalence was declared by the applicant in case the 90% CI were within 0.80 – 1.25 for AUC and Cmax.

- **Results**

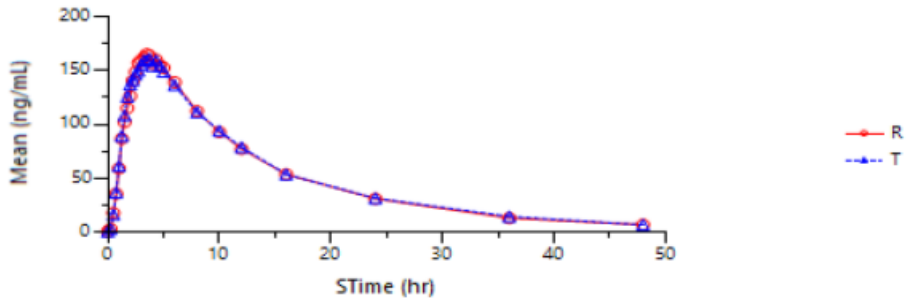
Sitagliptin:
The pharmacokinetic variables of sitagliptin of the Test and the Reference are shown in table PK 1 and the mean sitagliptin plasma concentration-time curves of Test and Reference in figure PK 1.

Tmax was not observed in the first sampling point. In addition, all pre-dose concentrations were below LOQ.
AUC_{0-t}/AUC_{0-inf} ratio was above 80%.

Table PK 1. The pharmacokinetic variables of sitagliptin of the Test and Reference (as mean ± s.d.; tmax as median (range)).

n=35	Sitagliptin 50/850 mg tablet dose 50 mg Test	Janumet® 50/850 mg tablet dose 50 mg Reference
$AUC_{(0-t)}$ (ng.h/ml)	2349 ± 306	2329 ± 386
$AUC_{(0-inf)}$ (ng.h/ml)	2448 ± 388	2431 ± 419
C_{max} (ng/ml)	196 ± 51	198 ± 63
t_{max} (h)	3.25 (1.25 – 12.00)	3.50 (1.25 – 6.05)
$t_{½}$ (h)	10.0 ± 1.3	10.2 ± 1.3

Figure PK 1. Mean sitagliptin plasma concentration-time curves for Test and Reference.



The results of the statistical analysis are listed in table PK 2.

Table PK 2. Statistical evaluation on sitagliptin pharmacokinetic variables

	$AUC_{(0-t)}$	C_{max}
Ratio's (test/ref)	1.01	1.00
90% confidence intervals:	0.99 – 1.04	0.92 – 1.07
Res. coeff. of variation	5.9%	18.7%

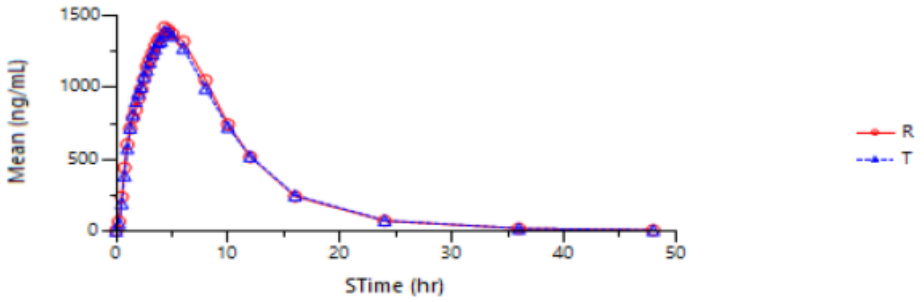
Metformin:
The pharmacokinetic variables of metformin of the Test and the Reference are shown in table PK 3 and the mean sitagliptin plasma concentration-time curves of Test and Reference in figure PK 2.

Tmax was not observed in the first sampling point. In addition, all pre-dose concentrations were below LOQ.
AUC_{0-t}/AUC_{0-inf} ratio was above 80%.

Table PK 3. The pharmacokinetic variables of metformin of the Test and Reference (as mean ± s.d.; tmax as median (range)).

n=35	Sitagliptin 50/850 mg tablet dose 850 mg Test	Janumet® 50/850 mg tablet dose 850 mg Reference
$AUC_{(0-t)}$ (ng.h/ml)	14710 ± 3570	14863 ± 3814
$AUC_{(0-inf)}$ (ng.h/ml)	14840 ± 3568	15002 ± 3807
C_{max} (ng/ml)	1499 ± 326	1516 ± 352
t_{max} (h)	4.33 (1.25 – 6.02)	4.33 (2.75 – 8.00)
$t_{½}$ (h)	5.1 ± 1.0	5.2 ± 1.3

Figure PK 2. Mean metformin plasma concentration-time curves for Test and Reference.



The results of the statistical analysis are listed in table PK 4.

Table PK 4. Statistical evaluation on metformin pharmacokinetic variables

	$AUC_{(0-t)}$	C_{max}
Ratio's (test/ref)	0.99	0.99
90% confidence intervals:	0.96 – 1.03	0.94 – 1.05
Res. coeff. of variation	9.8%	13.7%

Safety

A total of 8 AE's (5 AE's of itching all over the body, 1 AE of nausea, 1 AE of rashes on both hands and one 1 AE of back pain) were reported by 5 subjects during the study.
There were no deaths nor any serious adverse events reported in this study.

Pharmacokinetic conclusion on study I

Based on the submitted bioequivalence study the Sitagliptin/Metformin 50/850 mg tablet is considered bioequivalent with the Janumet® 50/850 mg tablet.
No concerns are identified.

III.2.2 Study II: single dose fed study, 50/1000 mg tablet

- **Study design**

This was a single-dose, randomised, crossover comparative bioequivalence study. Thirty-six male healthy subjects, aged 22 – 44 years, were dosed in this study. A standardized high fat and high calorie breakfast which was served to all the subjects at about 30 minutes prior to drug administration. Subjects were instructed to finish the high fat and high calorie breakfast within 30 minutes. No food was allowed for at least 4.00 hours post-dose. Subjects received a single dose (50/850 mg; 1 x 50/850 mg tablet) of the Test and Reference sitagliptin/metformin formulation. The tablets were administered in solid form with 240 ml of 20% glucose solution after an overnight fast. After drug administration to avoid hypoglycemia, subjects were administered 60 ml of 20% glucose solution in drinking water every 30 minutes for up to 4 hours post dose.
The washout period was 12 days.

Further information is listed below:
Title:
An open label, balanced, randomized, two-treatment, two-period, single dose, crossover, oral bioequivalence study of Sitagliptin and Metformin Hydrochloride 50mg/1000mg film-coated tablets of Rontis Hellas S.A., Greece, compared to Janumet® (sitagliptin and metformin hydrochloride) film-coated tablets 50mg/1000mg of Merck Sharp & Dohme B.V., The Netherlands, in healthy, adult, human volunteers under fed conditions.

Blood samples were taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.33, 4.67, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products. Samples were collected in tubes containing K_2EDTA and were centrifuged at 3000 rpm for 10 min under refrigerated conditions (4°C). Plasma samples were stored at -20ºC until analysis.

- Test and reference products

Sitagliptin/Metformin 50/1000 tablets have been compared to Janumet 50/1000 mg tablets.

Population(s) studied
Thirty-six healthy male subjects, aged 22 – 44 years, were dosed in Period I of this study.
One subject was withdrawn after dosing in Period 2 due to vomiting.
One subject was withdrawn after dosing in Period I due to an AE.
One subject did not check in for Period 2.
33 subjects completed the study and were included in the analysis.

- Analytical methods

Sitagliptin:
Plasma samples (K_2EDTA) were analysed for sitagliptin (together with metformin) using LC-MS/MS. The method was validated (K_2EDTA) and a validation report has been provided.
The calibration curve for sitagliptin ranged from about 3 – 1502 ng/ml. A weighted ($1/C^2$) linear regression was performed to determine the concentration of the analyte. Within-run and between-run accuracy and precision were tested on sitagliptin QC sample concentrations of about 3.0, 8.7, 94, 188, 526 and 1141 ng/ml during validation and at about 8.7, 94, 188, 526 and 1140 ng/ml during subject sample analysis.

Selectivity was demonstrated in processed blank plasma samples from 8 different sources, including 1 haemolysed sample and 1 lipemic sample. No endogenous interference was observed with the analytical peak or with that of the internal standard (sitagliptin-d4).
No interference was observed with metformin, metformin-d6, diclofenac, paracetamol, nicotine, caffeine, ondansetron and ranitidine.

Accuracy and precision obtained during validation is shown below:

Between-run precision:	1.7 – 7.2%
Between-run accuracy:	97.2 – 103.1%
Within-run precision:	0.2 – 13.1%
Within-run accuracy:	93.9 – 107.6%

Dilution of samples by a factor 3 and 5 did not affect the accuracy and precision.
No matrix effect (IS-normalised) is observed.
No carry-over is observed.

The stability results, i.e. blood (2h at room temperature), long term stability (134 days at -20°C and -70°C), short term stability (18h30min at room temperature), autosampler stability (119 at 5°C), 5 freeze/thaw cycles stability, and stock solution stability, showed that the analyte is stable under these consitions.

Accuracy and precision obtained during analysis of subjects samples is shown below.

Between-run precision:	1.8 – 2.9%
Between-run accuracy:	99.1 – 100.6%

Plasma samples were stored at -20ºC for 22 days.

1 subject sample had to be reanalysed, due to internal standard repsonse variation.

Incurred sample reanalysis on 153 samples showed good reproducibility (n=152 (99.3%) within the criteria).

Analytical chromatograms were included in the dossier. There were no trends in the IS responses.

Metformin:
Plasma samples (K_2EDTA) were analysed for metformin (together with sitagliptin) using LC-MS/MS. The method was validated (K_2EDTA) and a validation report has been provided.
The calibration curve for sitagliptin ranged from about 10 – 5003 ng/ml. A weighted ($1/C^2$) linear regression was performed to determine the concentration of the analyte. Within-run and between-run accuracy and precision were tested on metformin QC sample concentrations of about 10, 29, 313, 626, 1753 and 3802 ng/ml during validation and at about 29, 313, 625, 1752 and 3800 ng/ml during subject sample analysis.

Selectivity was demonstrated in processed blank plasma samples from 8 different sources, including 1 haemolysed sample and 1 lipemic sample. No endogenous interference was observed with the analytical peak or with that of the internal standard (metformin-d6).
No interference was observed with sitagliptin, sitagliptin-d4, diclofenac, paracetamol, nicotine, caffeine, ondansetron and ranitidine.

Accuracy and precision obtained during validation is shown below:

Between-run precision:	3.5 – 6.4%
Between-run accuracy:	98.7 – 106.0%
Within-run precision:	0.4 – 9.7%

Within-run accuracy: 94.8 – 110.2%

Dilution of samples by a factor 3 and 5 did not affect the accuracy and precision.
No matrix effect (IS-normalised) is observed.
No carry-over is observed.

The stability results, i.e. blood (2h at room temperature), long term stability (134 days at -20°C and -70°C), short term stability (18h30min at room temperature), autosampler stability (119 at 5°C), 5 freeze/thaw cycles stability, and stock solution stability, showed that the analyte is stable under these conditions.

Accuracy and precision obtained during analysis of subjects samples is shown below.

Between-run precision: 2.2 – 3.7%
Between-run accuracy: 97.0 – 101.1%

Plasma samples were stored at -20ºC for 22 days.

4 subject samples had to be reanalysed, due to internal standard response variation.

Incurred sample reanalysis on 153 samples showed good reproducibility (n=153 (100.0%) within the criteria).

Analytical chromatograms were included in the dossier. There were no trends in the IS responses.

- Pharmacokinetic Variables

Sitagliptin and metformin AUC was calculated by the linear trapezoidal method. C_{max} and t_{max} were derived directly from concentration-time-curve. Elimination rate constant was estimated from the slope of the regression line using the terminal data points of the semi-logarithmic plasma concentration - time curve. $T_{½}$ was calculated as $0.693/k_{el}$.

- Statistical methods

The 90% confidence intervals for the ratio of Test formulation over the Reference formulation were calculated for ln-transformed C_{max} and $AUC_{(0-t)}$ by ANOVA using SAS. Treatment, period, sequence and subjects within sequence were included as effects in the analysis.

Bioequivalence was declared by the applicant in case the 90% CI were within 0.80 – 1.25 for AUC and C_{max}.

- **Results**

Sitagliptin:
The pharmacokinetic variables of sitagliptin of the Test and the Reference are shown in table PK 5 and the mean sitagliptin plasma concentration-time curves of Test and Reference in figure PK 3.

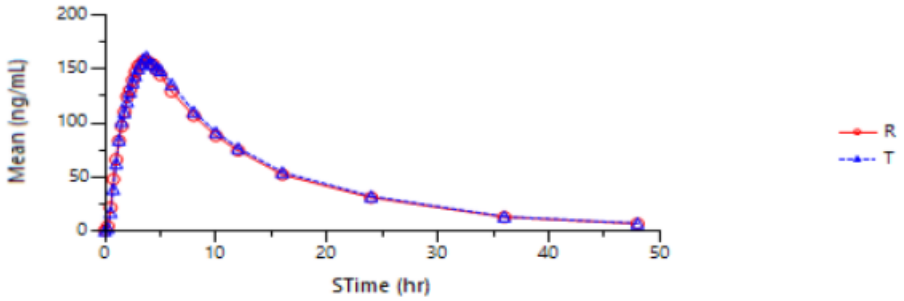
Tmax was not observed in the first sampling point. In addition, all pre-dose concentrations were below LOQ.
AUC_{0-t}/AUC_{0-inf} ratio was above 80%.

Table PK 5. The pharmacokinetic variables of sitagliptin of the Test and Reference (as mean ± s.d.; tmax as median (range)).

n=33	Sitagliptin 50/1000 mg tablet	Janumet® 50/1000 mg tablet

	dose 50 mg Test	dose 50 mg Reference
$AUC_{(0-t)}$ (ng.h/ml)	2319 ± 408	2253 ± 407
$AUC_{(0-inf)}$ (ng.h/ml)	2423 ± 441	2352 ± 440
C_{max} (ng/ml)	189 ± 49	187 ± 54
t_{max} (h)	3.50 (1.00 – 8.00)	3.25 (1.00 – 8.00)
$t_{½}$ (h)	10.3 ± 1.4	10.2 ± 1.5

Figure PK 3. Mean sitagliptin plasma concentration-time curves for Test and Reference.



The results of the statistical analysis are listed in table PK 6.

Table PK 6. Statistical evaluation on sitagliptin pharmacokinetic variables

	$AUC_{(0-t)}$	C_{max}
Ratio's (test/ref)	1.03	1.03
90% confidence intervals:	1.01 – 1.05	0.96 – 1.10
Res. coeff. of variation	4.9%	16.3%

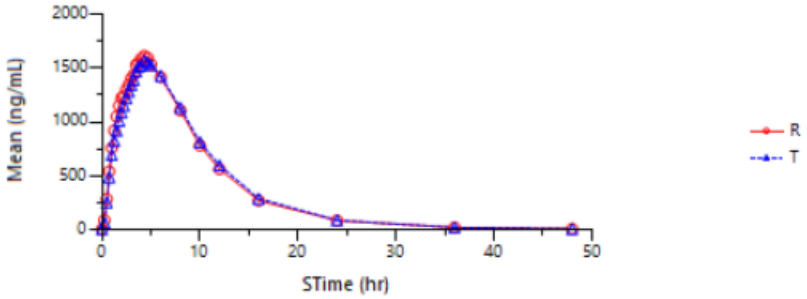
Metformin:
The pharmacokinetic variables of metformin of the Test and the Reference are shown in table PK 7 and the mean sitagliptin plasma concentration-time curves of Test and Reference in figure PK 4.

Tmax was not observed in the first sampling point. In addition, all pre-dose concentrations were below LOQ.
AUC_{0-t}/AUC_{0-inf} ratio was above 80%.

Table PK 7. The pharmacokinetic variables of metformin of the Test and Reference (as mean ± s.d.; tmax as median (range)).

n=33	Sitagliptin 50/1000 mg tablet dose 1000 mg Test	Janumet® 50/1000 mg tablet dose 1000 mg Reference
$AUC_{(0-t)}$ (ng.h/ml)	16676 ± 3881	16633 ± 3793
$AUC_{(0-inf)}$ (ng.h/ml)	16832 ± 3866	16788 ± 3790
C_{max} (ng/ml)	1726 ± 426	1782 ± 472
t_{max} (h)	4.33 (1.00 – 8.00)	4.33 (1.50 – 8.00)
$t_{½}$ (h)	5.1 ± 1.6	5.3 ± 2.0

Figure PK 4. Mean metformin plasma concentration-time curves for Test and Reference.



The results of the statistical analysis are listed in table PK 8.

Table PK 8. Statistical evaluation on metformin pharmacokinetic variables

	$AUC_{(0-t)}$	C_{max}
Ratio's (test/ref)	1.00	0.97
90% confidence intervals:	0.96 – 1.04	0.92 – 1.02
Res. coeff. of variation	10.0%	12.6%

Safety:
A total of five AE's (two AE's of vomiting, one AE of nausea, one AE of itching all over the body and one AE of abdominal pain) were reported by 4 subjects during the study. There were no deaths nor any serious adverse events reported in this study.

- **Pharmacokinetic conclusion**

Based on the submitted bioequivalence study the Sitagliptin/Metformin 50/1000 mg tablet is considered bioequivalent with the Janumet® 50/1000 mg tablet.
No concerns are identified.

III.3 Benefit-Risk assessment

Based on the submitted bioequivalence study, Sitagliptine/Metformine HCl Sandoz 50/850 mg film coated tablets and the Sitagliptine/Metformine HCl Sandoz 50/1000 mg film coated tablets are considered bioequivalent with Januvia 50/850 mg and 50/1000 mg film-coated tablets, respectively.

No concerns are identified.