COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5395/001 & 002/DC

19 May 2022

This module reflects the scientific discussion for the approval of Sipactimet. The procedure was finalised at 10 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 Sipactimet 50 mg/850 mg and 50 mg / 1000 mg, film-coated tablets, from Heaton k.s.

Sipactimet 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.

Sipactimet 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.

Sipactimet 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.

Sipactimet 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 which has been authorised in the EU via the centralised procedure (EU/1/08/455).

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

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

II. QUALITY ASPECTS

II.1 Introduction

Sipactimet 50 mg/850 mg film-coated tablets
Pink, capsule-shaped, biconvex, film-coated tablet, with "585" engraved on one side and break line on the other side.

Sipactimet 50 mg/1000 mg film-coated tablets

Red, capsule-shaped, biconvex, film-coated tablet, with "5100" engraved on one side and break line on the other side.

Sipactimet contains as active substance sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin, as well as 850 mg or 1000 mg of metformin hydrochloride respectively.

The tablets are packed in opaque PVC/PE/PVDC and OPA/Alu/PVC – aluminum blisters.

The excipients are:

Tablet core – povidone (K-value 27-32), sodium laurylsulphate, cellulose – microcrystalline (type 102) and magnesium stearate.

Film coating – polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide red (E172), iron oxide black (E172) **(50 mg/850 mg strength only)** and iron oxide yellow **(E172) (50 mg/1000 mg strength only).**

II.2 Drug Substance

Sitagliptin hydrochloride monohydrate
The first active substance is sitagliptin hydrochloride monohydrate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The Ph.Eur. 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 hexane. It has one chiral center. The R-enantiomer is the active form and used. The S-form is controlled as impurity. Sitagliptin hydrochloride monohydrate exhibits polymorphism, the crystalline form is used and is consistently produced.

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 of sitagliptin hydrochloride monohydrate comprises of seven steps. The process has been described in sufficient detail. The starting materials are acceptable. Batch 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 consists of in-house methods and general methods found in the Ph.Eur. This is considered to be adequate. Batch analytical data demonstrating compliance with this specification have been provided for three batches. The risk assessment regarding elemental impurities demonstrated that the levels of all elemental impurities to be tested for oral products and are below 30% of the ICH Q3D limit.

Stability of drug substance

Stability data on the active substance has been provided for eight batches stored at long term (25ºC / 60% RH) for 48 months and for three batches stored at accelerated conditions (40ºC / 75% RH) for six months in accordance with applicable European guidelines demonstrating the stability of the active substance for 48 months. Based on these results and in compliance with the ICH Q1E Guideline on Evaluation of Stability Data, where the proposed retest period can be up to 12 months the period covered by long-term data, a re-test period of 60 months is acceptable when protected from light in the original packaging with no special storage conditions regarding temperature and humidity.

Metformin hydrochloride

The second active substance is metformin hydrochloride, an established active substance described in the Ph.Eur. Metformin hydrochloride is described as white to almost white crystals and is freely soluble in water, slightly soluble in ethanol (96%) and practically insoluble in acetone and methylene chloride. The absence of additional specifications for polymorphism is justified.

The CEP procedure is used for this 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.

Manufacturing process

A CEP has 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 the CEP. Additionally, the MAH submitted extra studies for microbiological purity and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for three batches from manufacturer I and nine batches from manufacturer II.

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 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 development of the product has been described, 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 Reflection paper on 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.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional wet-granulation manufacturing process comprised of blending, wet granulation, blending and lubrication, and compression- and coating of the tablets. The manufacturing process is described in sufficient detail and is in line with the results of the optimisation studies. A hold time for the bulk tablets has been validated. Process validation data on the product have been presented for three batches from each manufacturing site in accordance with the relevant European guidelines.

Control of excipients

For the Ready-for-use mixtures in-house specifications are defined. These specifications are acceptable. The other excipients comply with the Ph. Eur. requirements.

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 substances, water content, average mass, dissolution, uniformity of dosage units (content uniformity for sitagliptin and mass variation for metformin), 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.

Satisfactory validation data for the analytical methods have been provided.

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

The provided risk evaluation for nitrosamine impurities is in accordance with line with the EMA document EMA/409815/2020. No potential risk for nitrosamine impurities was identified.

Stability of drug product

Stability data on the product have been provided for three batches for each strength from each manufacturer stored at long term (25°C/60% RH) for 18 months, at intermediate (30°C/65% RH) for 12 months and at accelerated conditions (40°C/75% RH) for six months in accordance with applicable European guidelines demonstrating the stability of the product for 21 months for the opaque PVC/PE/PVDC -aluminum blister and two years for the OPA/Alu/PVC- Aluminium blisters. Photostability data provided are in line with ICH Q1B. The product can be considered as photostable. On basis of the data submitted, a shelf life was granted of 21 months for the opaque PVC/PE/PVDC -aluminum blister when stored under 30 °C and two years for the OPA/Alu/PVC- Aluminium blisters with no special storage conditions.

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 Sipactimet 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 Sipactimet 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 & 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 has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sipactimet 50 mg/850 mg and 50 mg/1000 mg, film-coated tablets (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (Merck Sharp & Dohme B.V., the Netherlands).

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

The design of the study is acceptable.

Sitagliptin hydrochloride may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sitagliptin hydrochloride. However, food decreases the extent and slightly delays the absorption of metformin hydrochloride. 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. The fed conditions of the performed studies are therefore justified.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

50 mg/850 mg strength

Design

An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fed conditions in 34 healthy male subjects, aged 20-39 years. Each subject received a single dose (50 mg/850 mg) of one of the two sitagliptin hydrochloride/metformin hydrochloride formulations. The tablet was orally administered with 240 ml water after intake of a high fat, high caloric breakfast (milk, egg, chicken, bread, butter and hash brown potatoes). There were two dosing periods, separated by a washout period of eight 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, 3.75, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

Results

All 34 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin hydrochloride (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)	$t_{1/2}$ (h)
Test	2190 ± 290	2268 ± 301	169 ± 29	4.25 (1.0 – 5.5)	9.7 ± 0.8
Reference	2158 ± 291	2242 ± 299	164 ± 31	4.5 (1.0 – 6.0)	10.0 ± 1.0
***Ratio (90% CI)**	101.50 (99.43 – 103.62)	--	103.10 (98.85 – 107.83)	--	--
CV (%)	5.0	--	11.0	--	--

$AUC_{0-\infty}$ 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*

Table 2. **Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin hydrochloride (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)	$t_{1/2}$ (h)
Test	13929 ± 3162	14189 ± 3118	1504 ± 316	4.5 (1.0 – 8.0)	4.6 ± 1.9
Reference	14475 ± 3174	14719 ± 3128	1527 ± 316	4.5 (1.0 – 8.0)	4.5 ± 0.6
***Ratio (90% CI)**	96.07 (92.24 - 100.06)	--	98.53 (94.76 - 102.45)	--	--
CV (%)	9.9	--	9.5	--	--

$AUC_{0-\infty}$ 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*

50 mg/1000 mg strength

Design

A open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study was carried out under fed conditions in 34 healthy male subjects, aged 21-41 years. Each subject received a single dose (50 mg/1000 mg) of one of the two sitagliptin hydrochloride/metformin hydrochloride formulations. The tablet was orally administered with 240 ml water after intake of a high fat, high caloric breakfast (milk, egg, chicken, bread, butter and hash brown potatoes). There were two dosing periods, separated by a washout period of 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, 3.75, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

Results

All 34 subjects were eligible for pharmacokinetic analysis.

Table 3. **Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin hydrochloride (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)	$t_{1/2}$ (h)

Test	2249 ± 328	2324 ± 348	193 ± 40	4.125 (1.25 – 6.0)	9.6 ± 1.1
Reference	2181 ± 330	2251 ± 347	185 ± 36	3.75 (1.25 – 7.0)	9.4 ± 1.0
***Ratio (90% CI)**	103.18 (101.15 – 105.24)	--	104.63 (98.84 – 110.75)	--	--
CV (%)	4.8	--	13.9	--	--

$AUC_{0-\infty}$ 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*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin hydrochloride (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)**	**$t_{1/2}$ (h)**
Test	17045 ± 3609	17254 ± 3593	1900 ± 450	4.5 (1.0 – 6.0)	4.9 ± 1.0
Reference	16627 ± 3471	16839 ± 3724	1854 ± 479	4.5 (1.0 – 6.0)	4.8 ± 0.9
***Ratio (90% CI)**	102.83 (98.96 – 106.85)	--	103.20 (96.65 – 110.20)	--	--
CV (%)	9.4	--	16.1	--	--

$AUC_{0-\infty}$ 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*

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 080 – 125%. Based on the submitted bioequivalence studies Sipactimet is considered bioequivalent with Janumet.

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 Sipactimet.

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 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 Janumet. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies 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 Janumet 50 mg/850 mg film-coated tablets (EMEA/H/C/000861) for content and Etoricoxib 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets (EL/H/0198/001-004) for design/layout/format. 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

Sipactimet 50 mg/850 mg and 50 mg / 1000 mg, film-coated tablets has a proven chemical-pharmaceutical quality and are generic forms of Janumet. 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sipactimet with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 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