CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Sitagliptin/Metformin HCS 50 mg/850 mg film-coated tablets
Sitagliptin/Metformin HCS 50 mg/1 000 mg film-coated tablets
sitagliptin/metformin hydrochloride

SK/H/0278/001-002/DC

Date: April 2025

This module reflects the scientific discussion for the approval of Sitagliptin/Metformin HCS. The procedure was finalised on 13 February 2023 (D210). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for **Sitagliptin/Metformin HCS 50 mg/850 mg and Sitagliptin/Metformin HCS 50 mg/1 000 mg** *(hereinafter Sitagliptin/Metformin HCS)* from HCS BV, Belgium.

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

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.

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.

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.

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.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as a film-coated tablet containing 50 mg of sitagliptin and 850 mg or 1,000 mg of metformin hydrochloride as active substances. Film-coated tablets are packed in OPA/Alu/PVC//Alu blisters or in PVC/PE/PVDC/PE/PVC//Alu blisters.

Available pack sizes are as follows:

Blister (OPA/Alu/PVC//Alu): 10, 14, 56, 60, 196, 200 film-coated tablets, in a box.
Blister (OPA/Alu/PVC//Alu), calendar pack: 14, 56, 196 film-coated tablets, in a box.
Blister (PVC/PE/PVDC/PE/PVC//Alu): 10, 14, 56, 60, 196, 200 film-coated tablets, in a box.
Blister (PVC/PE/PVDC/PE/PVC//Alu), calendar pack: 14, 56, 196 film-coated tablets, in a box.

Description of a pharmaceutical form:

Sitagliptin/Metformin HCS 50 mg/850 mg film-coated tablets
Pink, oval, biconvex, film coated tablets marked with C4 on one side of the tablet (dimensions approx.: 20 x 11 mm).

Sitagliptin/Metformin HCS 50 mg/1000 mg film-coated tablets
Dark pink, oval, biconvex, film coated tablets marked with C3 on one side of the tablet (dimensions approx.: 21 x 11 mm).

The other ingredients are:

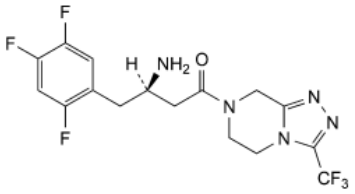
Tablet core
povidone
microcrystalline cellulose
mannitol
sodium laurilsulfate
magnesium stearate

Film-coating
hypromellose
titanium dioxide (E171)
talc
propylene glycol
red ferric oxide (E172)

II.2 Drug Substances

Sitagliptin

Active substance structure:



Empirical formula: $C_{16}H_{15}F_6N_5O$

Chemical name: ((3*R*)-3-Amino-1-(3-(trifluoromethy1)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-y1)-4-(2,4,5-trifluorophenyl)butan-l-one

Appearance: White or almost white powder.

Solubility: Soluble in anhydrous ethanol (33.3-100 mg/mL), slightly soluble in water and in heptane(1-10 mg/mL), freely soluble in methanol, acetone, *N*,*N*-dimethylformamide, methylene chloride (100-1000 mg/mL) soluble in 0.1M aq. HCl (33.3-100 mg/mL), very slightly soluble in 0.1M aq. NaOH (0.1-1 mg/mL), freely soluble in acetate buffer solution pH 4.5 and in phosphate buffer solution (100-1000 mg/mL).

Chirality: There is one chiral atom in the molecule (*R*-isomer), enantiomer (*S*-isomer, impurity A).

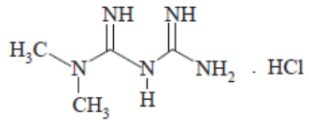
Manufacturing: Active substance master file (ASMF) procedure was followed and approved via an European ASMF work-sharing procedure for this drug substance.

Specification: The specification of the active pharmaceutical ingredient (API) includes test methods in accordance with the Ph.Eur. monograph for sitagliptin phosphate monohydrate and additionally tests for residual solvents and microbiological quality.

Stability: The proposed re-test period of 24 months was accepted.

Metformin hydrochloride

Active substance structure:



Empirical formula: $C_4H_{11}N_5$ .HCl

Chemical name: 1-carbamimidamido-N,N-dimethylmethanimidamide

Appearance: White or almost white crystals.

Solubility: Freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.

Chirality: Metformin does not possess chiral carbon centre.

Manufacturing: Information on the manufacturing process and process controls has been supplied to, and approved by, the European Directorate for the Quality of Medicines (EDQM) in relation to the Certificate of Suitability Procedures (CEP) for metformin hydrochloride (Ph. Eur.) from two manufacturers.

Specification: The specification of the API metformin hydrochloride includes test methods in accordance with the Ph.Eur. monograph for metformin hydrochloride (0931) and additionally tests for residual solvents, in line with the CEP and microbiological quality.

Stability: The re-test period is 5 years or 2 years from first manufacturer or 5 years, as supported by the stability data provided from second manufacturer.

II.3 Medicinal Product

Pharmaceutical development

The finished product was developed as a generic of Janumet film-coated tablets and it is manufactured in two strengths 50 mg/850 mg and 50 mg/1,000 mg.

The development of the product was described in sufficient detail. These were duplicate applications of the same dossier as approved in procedure SK/H/0242/001-002/DC. The dossier has undergone several variations since the first approval. To optimise the final formulation of the finished product, lubricant sodium stearyl fumarate was replaced by magnesium stearate. To ensure a better differentiation between strengths a minor change was made in the quantitative and qualitative composition of the film-coating of the lower strength 50 mg/850 mg. Iron oxide yellow was removed from the composition and the amount of iron oxide red was reduced.

Manufacturing

The finished product is manufactured by fluid-bed granulation and a detailed description of the process has been provided in the dossier. In brief, it involves manufacturing of granulate, sieving, manufacturing of compression mixture, tabletting and film coating. Process validation was performed on a batch size of 100,000 tablets of each strength.

Specification

The finished product release and shelf-life specifications include appropriate tests and limits for appearance (visual), identification of sitagliptin and metformin hydrochloride (HPLC/TLC, in-house), uniformity of dosage units – content uniformity of sitagliptin (Ph.Eur.), uniformity of dosage units – mass variation of metformin hydrochloride (Ph.Eur.), impurities of sitagliptin and metformin

hydrochloride (in-house), residual solvent – ethanol (in-house), dissolution of sitagliptin and metformin hydrochloride (Ph.Eur.), content of sitagliptin and metformin hydrochloride (in-house), N-nitrosodimethylamine (NDMA) (in-house), and microbiological quality (Ph.Eur.). The proposed specification for the finished product is in line with ICH Q6A, where relevant.

Stability

Stability data were provided for three batches of each strength under long-term, intermediate and accelerated conditions which were packed in OPA/Al/PVC-Al blister and in PVC/PE/PVDC/PE/PVC-Alu blister as proposed for marketing. The proposed shelf life of 2 years (24 months) was accepted with following storage conditions:

OPA/Alu/PVC//Alu blisters:
This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

PVC/PE/PVDC/PE/PVC//Alu blisters:
Do not store above 30°C. Store in the original package in order to protect from moisture.

II.4 Discussion on chemical, pharmaceutical and biological aspects

From a quality point of view the dossier was adequately presented.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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Pharmacodynamic, pharmacokinetic and toxicological properties of metformin hydrochloride and sitagliptin are well known. As metformin hydrochloride and sitagliptin are widely used, well-known active substances, the applicant has not provided additional studies, and further studies were not required. The overview based on literature review was, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The applicant has provided ERA data (literature based and published European Public Assessment Report (EPAR) of Janumet and other publicly available ERA assessments) and discussion for both active substances (sitagliptin and metformin hydrochloride).

The conclusions are reflected in the SmPC of the generic product, which contains no special precautions (or mitigation measures) regarding the environment, except for the standard disposal warning.

III.3 Discussion on the non-clinical aspects

Sufficient references to published non-clinical data were provided for this generic application, which was considered adequate. Presented literature data did not indicate that authorisation of proposed generic medicinal product would pose a significant risk for the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview based on the scientific literature on the clinical pharmacology, efficacy and safety was adequate. No further clinical studies were required, besides two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

To support the application, the applicant has submitted two bioequivalence studies; one with the 50 mg/850 mg strength (study no. 19-632 [180284] and one with the 50 mg/1,000 mg strength (study no. 18-600 [180283]. Both studies were performed under fed conditions.

1. Pharmacokinetic study - 18-600 [180283]

This study was designed as single center, randomized, open-label, 2-way crossover bioequivalence study of two sitagliptin/metformin 50 mg/1,000 mg film-coated tablet formulations (test or reference product) in healthy male and female volunteers under fed conditions.

In each study period, subjects received a single oral dose of 50 mg/1,000 mg of sitagliptin-metformin film-coated tablet (test or reference product) 30 min after high-fat, high calorie meal of between 800 to 1,000 calories. Wash-out period was 7 days. There were 30 subjects dosed in the bioequivalence study (14 females and 16 males).
27 subjects for sitagliptin and 28 subjects for metformin were included in the pharmacokinetic and statistical analysis for AUC. For both sitagliptin and metformin 28 subjects were included in the final analysis of C_{max}.

Bioanalytical method for both active substances (sitagliptin, metformin) and validation of the bioanalytical method

The pre-study validation of the analytical methods is satisfactory and demonstrated adequate precision and accuracy (both intra- and inter-run) within the calibration range, which showed adequate selectivity, sensitivity, no matrix effect and no-carry-over effect. For analyte sitagliptin the validation parameters were performed on two instruments (Triple Quad 5500 and API Sciex 4000). Analyte stability for both sitagliptin and metformin was shown at various conditions during storage (freeze/thaw cycle), sample preparation and analysis. The information given by the bioanalytical study report confirmed that the analytical method established is suitable to determine sitagliptin and metformin in human plasma and provided accurate, precise and reproducible results. The acceptance criteria laid down in the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.*) were fulfilled.

Pharmacokinetic variables

The pharmacokinetic parameters of this trial were C_{max}, AUC_{0-t} (main pharmacokinetic parameters), T_{max}, $AUC_{0-\infty}$, $AUC_{0-t/\infty}$ and Thalf.

Results

Table 1. *Pharmacokinetics data for sitagliptin in study 18-600 (180283)*

Pharmacokinetics Parameters	Arithmetic Mean (±SD)	
	Test product	Reference product
$AUC_{(0-t)}$ (ng·h/mL)	1739.88 (±260.09)	1722.89 (±287.27)
$AUC_{(0-\infty)}$ (ng·h/mL)	1803.75 (±268.07)	1795.96 (±316.14)
C_{max} (ng/mL)	174.87 (±47.85)	173.14 (±43.10)
T_{max} (hr) [1]	2.987 (0.737, 6.002)	2.988 (0.740, 5.000)

[1] Median (Min, Max)

Table 2. *Pharmacokinetics data for metformin in study 18-600 (180283)*

Pharmacokinetics Parameters	Arithmetic Mean (±SD)	
	Test product	Reference product
$AUC_{(0-t)}$ (ng·h/mL)	14818.88 (±3181.59)	14250.19 (±3255.66)
$AUC_{(0-\infty)}$ (ng·h/mL)	15022.21 (±3202.70)	14478.66 (±3251.99)
C_{max} (ng/mL)	1714.13 (±394.83)	1657.36 (±375.33)
T_{max} (hr) [1]	4.249 (1.005, 7.957)	4.490 (0.994, 8.031)

[1] Median (Min, Max)

Table 3. *Bioequivalence evaluation of sitagliptin in study 18-600 (180283)*

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-t)}$ (ng·h/mL)	101.18%	99.75% to 102.63%	3.05%
$AUC_{(0-\infty)}$ (ng·h/mL)	100.75%	98.94% to 102.59%	3.90%
C_{max} (ng/mL)	100.52%	93.36% to 108.24%	16.29%

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

Table 4. *Bioequivalence evaluation of metformin in study 18-600 (180283)*

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-t)}$ (ng·h/mL)	104.23%	101.10% to 107.46%	6.68%
$AUC_{(0-\infty)}$ (ng·h/mL)	103.93%	101.09% to 106.86%	6.08%
C_{max} (ng/mL)	103.31%	99.08% to 107.73%	9.17%

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

AUC_{0-t}	Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

The 90 % confidence intervals of the ratios are within the acceptance range (0.80–1.25) for the ln transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The results of the study show bioequivalence between test and reference product when administered under fed condition.

Safety evaluation

A total of 34 treatment emergent adverse events (TEAEs) were reported by 17 of the 30 subjects who received at least one dose of the study medication (safety population). No deaths, serious or significant adverse effects (AEs) were reported during this study.

2. Pharmacokinetic study 19-632 [180284]

This study was designed as single centre, randomised, open-label, 2-way crossover bioequivalence study of two sitagliptin/metformin 50 mg/850 mg film-coated tablet formulations (test or reference product) in healthy male and female volunteers under fed conditions.

In each study period, subjects received a single oral dose of 50 mg/850 mg of sitagliptin-metformin film-coated tablet (test or reference product) 30 min after high-fat, high calorie meal of between 800 to 1,000 calories. Wash-out period was 7 days.

There were 30 subjects randomised and dosed in the bioequivalence study and included in the safety population (15 females and 15 males); of these, 29 subjects completed the study.
29 subjects for sitagliptin and 29 subjects for metformin were included in the pharmacokinetic and statistical analysis for AUC. For both sitagliptin and metformin 29 subjects were included in the final analysis of C_{max}.

Bioanalytical method for both active substances (sitagliptin, metformin) and validation of the bioanalytical method

The pre-study validation of the analytical methods was satisfactory and demonstrated adequate precision and accuracy (both intra- and inter-run) within the calibration range, which showed and adequate selectivity, sensitivity, no matrix effect and no-carry-over effect. Analyte stability for both sitagliptin and metformin was shown at various conditions during storage (freeze/thaw cycle), sample preparation and analysis. The applied analytical method is acceptable and validated. Statement on GLP compliance was provided. Handling of samples was adequate. For analyte sitagliptin the validation parameters were performed on two instruments (Triple Quad 5500 and API Sciex 4000).

Pharmacokinetic variables

The pharmacokinetic parameters of this trial were C_{max}, AUC_{0-t} (main pharmacokinetic parameters), T_{max}, $AUC_{0-\infty}$, $AUC_{0-t/\infty}$ and Thalf.

Results

Table 5. *Pharmacokinetics data for sitagliptin in study 19-632 (180284)*

Pharmacokinetics Parameters	Arithmetic Mean (±SD)	
	Test product	Reference product
$AUC_{(0-t)}$ (ng·h/mL)	1827.82 (±357.89)	1796.22 (±366.31)
$AUC_{(0-\infty)}$ (ng·h/mL)	1908.60 (±377.43)	1871.55 (±381.21)
C_{max} (ng/mL)	167.32 (±41.67)	163.98 (±47.67)
T_{max} (hr) [1]	2.990 (0.986, 5.991)	3.010 (0.987, 5.118)

[1] Median, (Min, Max)

Table 6. *Pharmacokinetics data for metformin in study 19-632 (180284)*

Pharmacokinetics Parameters	Arithmetic Mean (±SD)	
	Test product	Reference product
$AUC_{(0-t)}$ (ng·h/mL)	14366.84 (±3101.29)	13973.47 (±3350.60)
$AUC_{(0-\infty)}$ (ng·h/mL)	14568.24 (±3150.69)	14161.68 (±3384.02)
C_{max} (ng/mL)	1535.45 (±322.20)	1498.86 (±309.60)
T_{max} (hr) [1]	4.988 (1.009, 7.961)	4.493 (2.670, 5.998)

[1] Median, (Min, Max)

Table 7. *Bioequivalence evaluation of sitagliptin in study 19-632 (180284)*

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-t)}$ (ng·h/mL)	101.90%	100.54% to 103.28%	3.00%
$AUC_{(0-\infty)}$ (ng·h/mL)	102.06%	100.73% to 103.41%	2.94%
C_{max} (ng/mL)	103.28%	95.32% to 111.90%	18.06%

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

Table 8. *Bioequivalence evaluation of metformin in study 19-632 (180284)*

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-t)}$ (ng·h/mL)	103.14%	99.86% to 106.53%	7.23%
$AUC_{(0-\infty)}$ (ng·h/mL)	103.17%	99.98% to 106.46%	7.02%
C_{max} (ng/mL)	102.18%	98.19% to 106.33%	8.91%

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

The 90 % confidence intervals of the ratios are within the acceptance range (0.80–1.25) for the ln transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The results of the study show bioequivalence between test and reference product when administered under fed condition.

Safety evaluation

A total of nine TEAEs were reported by six of the 30 subjects who received at least one dose of the study medication (safety population). No deaths, serious or significant AEs were reported during this study. One (1) subject had clinically significant safety measurement results (biochemistry) during the

study; however, data from the subjects completing study exit procedures (including laboratory tests, vital signs measurements, and urine pregnancy test) confirmed the absence of significant changes in the subject's state of health.

Conclusion on bioequivalence studies

Based on the submitted bioequivalence studies Sitagliptin/Metformin HCS 50 mg/850 mg and Sitagliptin/Metformin HCS 50 mg/1 000 mg are considered bioequivalent with Janumet 50 mg/850 mg and 50 mg/1 000 mg.

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 Sitagliptin/Metformin HCS.

- 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

IV.4 Discussion on the clinical aspects

Submitted clinical dossier was of sufficient quality. Submitted data supported the chosen legal basis "generic application".
Based on the results of submitted bioequivalence studies it was concluded, that Sitagliptin/Metformin HCS 50 mg/850 mg and Sitagliptin/Metformin HCS 50 mg/1 000 mg from by HCS BV, Belgium are considered bioequivalent with Janumet 50 mg/850 mg and 50 mg/1 000 mg from Merck Sharp & Dohme B.V., the Netherlands.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed based on a bridging report.

The content and key safety messages in Sitagliptin/Metformin HCS 50 mg/850 mg and 50 mg/1 000 mg film-coated tablets were the same as in the PL of reference medical product Janumet, therefore, the applicant proposed bridging only for design and layout.
The applicant claimed to use ''house style'' design for all of their products, meaning the layout/design of the daughter leaflet is identical to previously assessed and accepted leaflets, for this procedure the applicant chose the parent leaflet of pregabalin hard capsules authorised via several DCPs: SI/H/0155/001-004, SI/H/0152/001-008, SI/H/0153/001-008, SI/H/0154/001-008, DE/H/4120/001-008.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This was an application for a marketing authorisation (MAA) of medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended. Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak

Republic acting as RMS. The applicant, Krka d.d., Novo mesto, Slovenia has submitted this MAA under procedural number SK/H/0278/001-002/DC.

Reference medicinal product was Janumet, film-coated tablets from Merck Sharp & Dohme B.V., the Netherlands authorised in the European Union via centralised procedure (EMEA/H/C/861) since 16 July 2008.

Based on the results of submitted bioequivalence studies it was concluded, that Sitagliptin/Metformin HCS 50 mg/850 mg and Sitagliptin/Metformin HCS 50 mg/1 000 mg from by HCS BV, Belgium are considered bioequivalent with Janumet 50 mg/850 mg and 50 mg/1 000 mg from Merck Sharp & Dohme B.V., the Netherlands.

Quality aspects of the dossier were adequately described; specifications of API sitagliptin were adequately demonstrated via an ASMF procedure and that of metformin hydrochloride were in line with monograph no. 0931 published under Ph. Eur. Finished medicinal product´s specifications are in line with ICH Q6A, where relevant.

There was no discussion in the CMDh. Agreement between the member states was reached during a written procedure. Based on submitted data the member states considered that the essential similarity with the reference medicinal product Janumet, film-coated tablets was adequately demonstrated and have, therefore, granted marketing authorisation. This decentralised procedure was positively concluded on 13 February 2023 (D210).