Public Assessment Report

Scientific discussion

Sitagliptin/Metformin Krka 50 mg/850 mg film-coated tablets
Sitagliptin/Metformin Krka 50 mg/1000 mg film-coated tablets

SIATGAVIA MET 50 mg/850 mg film-coated tablets
SITAGAVIA MET 50 mg/1000 mg film-coated tablets

Maymetsi 50 mg/850 mg film-coated tablets
Maymetsi 50 mg/1000 mg film-coated tablets

sitagliptin/metformin hydrochlorid

SK/H/0240/001-002/DC
SK/H/0241/001-002/DC
SK/H/0242/001-002/DC

Date: 03/2021

This module reflects the scientific discussion for the approval of Sitagliptin/Metfromin Krka. The procedure was finalised at 19.11.2020 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 Krka 50 mg/850 mg film-coated tablets
Sitagliptin/Metformin Krka 50 mg/1000 mg film-coated tablets
SIATGAVIA MET 50 mg/850 mg film-coated tablets
SITAGAVIA MET 50 mg/1000 mg film-coated tablets
Maymetsi 50 mg/850 mg film-coated tablets
Maymetsi 50 mg/1000 mg film-coated tablets

from **Krka, d.d., Novo mesto, Slovenia**

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

<Invented name> 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.

<Invented name> 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.

<Invented name> 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.

<Invented name> 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 procedures concerns a generic application claiming essential similarity with the innovator product Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (EU/1/08/455) marketed by Merck Sharp & Dohme B.V, which has been authorised in the European Union via the centralised procedure since 16 July 2008.

Involved Concerned Member States:

SK/H/0240/001-002/DC
CMSs: AT, BE, DK, ES, FI, FR, IE, IS, IT, NO, PT, SE

SK/H/0241/001-002/DC
CMS: DE

SK/H/0242/001-002/DC
CMSs: BG, CY, CZ, EE, EL,HR, HU, LT, LV,PL, RO, SI

The marketing authorisations has been granted pursuant to Article10 (1) generic application of Directive 2001/83/EC."

*Name **Sitagliptin/Metfromin Krka** is used throughout this report and it refers to all above stated authorized medicinal products.*

II. QUALITY ASPECTS

II.1 Introduction

Sitagliptin/Metformin Krka 50 mg/850 mg film-coated tablets:
off pink, oval, biconvex, film coated tablets marked with C4 on one side of the tablet (dimensions approx.: 20 x 11 mm).
Each film-coated tablet contains 50 mg sitagliptin and 850 mg of metformin hydrochloride.

Sitagliptin/Metformin Krka 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).
Each film-coated tablet contains 50 mg sitagliptin and 1000 mg of metformin hydrochloride

The film-coated tablets are packed in OPA/Alu/PVC//Alu blister and calendar pack OPA/Alu/PVC//Alu blister.

The excipients are:
Tablet core
povidone
microcrystalline cellulose
mannitol
sodium laurilsulfate
sodium stearyl fumarate

Film coating
hypromellose
titanium dioxide (E171)
talc
propylene glycol
red ferric oxide (E172)
yellow ferric oxide (E172) *(only for 50 mg/850 mg)*

II.2 Drug Substance

Sitagliptin

Sitagliptin is a synthetic substance. There is no Ph.Eur. monograph for sitagliptin base though there is one for its salt: sitagliptin phosphate monohydrate.

Molecular Formula: $C_{16}H_{15}F_6N_5O$

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 0.1 M aq. HCl (33.3-100 mg/mL), very slightly soluble in 0.1 M 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)

Melting point: 110-120 °C

Hygroscopicity: sitagliptin is not hygroscopic

Isomerism: there is one chiral atom in the molecule (*R*-isomer), enantiomer (*S*-isomer, impurity A) is routinely controlled by the active substance manufacturer.

Polymorphism anhydrous crystalline forms found to exist, Form I is manufactured by the manufacturer

Manufacturing

The **ASMF procedure** was used for the active substance sitagliptin.
Competent Authorities 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.
A block scheme of the manufacturing process consisting of eight to nine manufacturing steps, depending on the site of the manufacture of the intermediate, was provided in the dossier and in the Applicant's part of the ASMF. A brief description of the manufacturing process was also included. The proposed API specification is considered adequate in order to ensure the quality of the substance to be used in the proposed finished product and it is accepted

Metformin hydrochloride

Metformin is a synthetic substance. There is a Ph.Eur. monograph for metformin hydrochloride (01/2017:0931)

Molecular Formula: $C_4H_{11}N_5.HCl$

Appearance: White or almost white crystals

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

Melting point: 222°C to 226°C

Hygroscopicity: metformin is not hygroscopic

Isomerism: Metformin doesn't exhibits optical isomerism.

Manufacturing:

Manufacturing of metformin hydrochloride is supported by valid Certificate of suitability (CEP). The specification of the 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. The active substance is stable for 5 years when stored under the stated conditions.

II.3 Medicinal Product

The development of the product is described in sufficient detail.

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, tableting and film coating. Process validation was performed on a batch size of 100,000 tablets of each strength

The proposed specification for the finished product is in line with ICH Q6A, where relevant, and is generally acceptable.

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 as proposed for marketing.

The proposed shelf life of 2 years (24 months) was accepted. The following storage instructions apply: “Store in the original package in order to protect from moisture.”

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of metformin and sitagliptin are well known. As metformin 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 is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sitagliptin/Metfromin Krka 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

The use of a different form i.e. base of sitagliptin compared to the innovator product (phosphate salt) is acceptable. It was agreed with the applicant that there are no pharmacological or toxicological objections against the use of this form of sitagliptin in the proposed indication compared to the phosphate salt.

Metformin and sitagliptin are two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in adult patients with

type 2 diabetes mellitus. **Sitagliptin** is an oral, potent, and selective dipeptidyl peptidase-IV (DPP-4) inhibitor, elevates GLP-1 levels, and markedly reduces glucose levels following an oral glucose load. **Metformin** is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Pharmacotherapeutic group: Drugs used in diabetes, Blood glucose lowering drugs, excl. insulins, ATC code: A10BD07.

IV.2 Pharmacokinetics

To support the application, the applicant has submitted two bioequivalence studies designed as randomized, open-label, 2-way crossover bioequivalence studies of two Sitagliptin/ Metformin film-coated tablet formulations (test or reference product) in healthy male and female volunteers under fed conditions.; one with the 50 mg/850 mg strength and one with the 50 mg/1000 mg strength.

The number and type of bioequivalence studies is sufficient for the applied product (an immediate release tablet formulation). Studies have been conducted for both requested strengths.

The applied analytical method is acceptable and validated. Handling of samples was adequate. Statistical method is well described and acceptable.

Statement on GCP compliance was provided.

Bioequivalence studies

Study I (strength 50 mg/1000 mg)
In each study period, subjects received a single oral dose of 50 mg / 1000 mg of sitagliptin-metformin film-coated tablet (test or reference product) 30 min after high-fat, high calorie meal of between 800 to 1000 calories.
The investigational products were administered orally in 2 periods with wash-out period of 7 days.
A blood samples of 4 mL (sitagliptin) and 3 mL (metformin) were collected for each subject at the check-in of period 1 (Sample 00) for the investigation of potential pre-dose concentrations of sitagliptin or metformin. This sample was not used for pharmacokinetic evaluations.
The following samples were analyzed for quantitation of sitagliptin (1 × 4 mL): prior to drug administration and 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post-dose.
The following samples were analyzed for quantitation of metformin (1 × 3 mL): prior to drug administration and 0.250, 0.500, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0 and 36.0 hours post-dose.

Results

There were 30 subjects dosed in the bioequivalence study (14 females and 16 males).
28 subjects were included in the pharmacokinetic and statistical analysis. All 30 subjects have been considered in the safety analysis.
Subject Nos. 18 and 19 were analysed for safety reason but were not included in the PK and statistical analyses since they experienced vomiting (8-hour 26 min post-dose) and liquid stools (10-hour 24 min post-dose), respectively which was in accordance with the study protocol.

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

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)

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
T_{max} Time until Cmax is reached

Table 2. Bioequivalence evaluation of sitagliptin in the study

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

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 4. Bioequivalence evaluation of metformin in study

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.

STUDY II (strength 50 mg/850 mg)
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 1000 calories.
The investigational products were administered orally in 2 periods with wash-out period of 7 days.
A blood samples of 4 mL (sitagliptin) and 3 mL (metformin) were collected for each subject at the check-in of period 1 (Sample 00) for the investigation of potential pre-dose concentrations of sitagliptin or metformin. This sample was not used for pharmacokinetic evaluations.
The following samples were analyzed for quantitation of sitagliptin (1 × 4 mL): prior to drug administration and 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 12.0, 16.0, 24.0, 36.0- and 48.0-hours post-dose.
The following samples were analyzed for quantitation of metformin (1 × 3 mL): prior to drug administration and 0.250, 0.500, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0- and 36.0-hours post-dose.

Results
Thirty (30) subjects were dosed in this study and included in the safety population; of these, 29 subjects completed the study. Subject No. 12 was discontinued from the study. In accordance with the study protocol, data from all subjects who completed the study and for whom the PK profile was adequately characterized were used for PK and statistical analyses (N=29). Data from Subject No. 12 who discontinued the study due to vomiting (PK reason) were presented.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for sitagliptin under fed condition

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)

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
T_{max} Time until Cmax is reached

Table 6. Bioequivalence evaluation of sitagliptin in the study

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 7. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for metformin under fed condition

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 8. Bioequivalence evaluation of metformin in study

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.

Conclusion on bioequivalence studies:

This studies are a fed studies, what is acceptable concerning the pharmaceutical form of the medicinal product. The meal composition was in accordance with the requirements of fed studies in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 Corr**).
Wash-out period (7 days; i.e. 5 times the expected half-life of each drug) was chosen long enough to avoid the carry-over effect. The sampling period (48 and 36 hrs respectively) is long enough concerning the T1/2 of sitagliptin and metformin (sitagliptin 12.4 hours, metformin 6.5 hours).

The 90 % confidence intervals of the ratios are within the acceptance range (0.80–1.25) for the ln transformed Cmax, AUC0-t and AUC0-∞. The results of the studies show bioequivalence between test and reference products when administered under fed condition.

Based on the submitted bioequivalence studies **Sitagliptin/Metformin Krka (**50 mg/1000 mg and 50 mg/850 mg) is considered bioequivalent with Janumet (50 mg/1000 mg and 50 mg/850 mg) film-coated tablets of Merck Sharp & Dohme Ltd. UK.

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 Krka*.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
The safety information in the proposed product information is aligned to the reference medicinal product. Routine risk minimisation was suggested, and no additional risk minimisation activities are proposed by the applicant, which was endorsed.

Table 9. Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	Lactic acidosis
Important potential risks	Pancreatic cancer
Missing information	Exposure during pregnancy and lactation

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Janumet. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference for design and layout to Pregabalin hard capsules. The user test of the parent leaflet has been assessed and accepted in DCP procedures SI/H/0155/01-04, SI/H/0152/01-08, SI/H/0153/01-08, SI/H/0154/01-08, DE/H/4120/01-08. The content and key safety messages in Sitagliptin/Metformin Krka are the same as in the PL of reference medical product Janumet. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sitagliptine/Metformin Krka with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19.11.2020