*CMDh/223/2005*
*February 2014*

# Public Assessment Report

# Scientific discussion

# Sitagliptin HCS 25 mg film-coated tablets
# Sitagliptin HCS 50 mg film-coated tablets
# Sitagliptin HCS 100 mg film-coated tablets
# Sitagliptin

# SK/H/0277/001-003/DC

# Date: April 2025

**This module reflects the scientific discussion for the approval of Sitagliptin HCS. The procedure was finalised on 14 January 2023 (D200). 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 HCS 25 mg film-coated tablets, Sitagliptin HCS 50 mg film-coated tablets, Sitagliptin HCS 100 mg film-coated tablets (*hereinafter Sitagliptin HCS*), from HCS BV, Belgium.

The product is indicated for adult patients with type 2 diabetes mellitus, Sitagliptin HCS is indicated to improve glycaemic control:

as monotherapy:

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with:

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.

- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.

- a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with:

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Sitagliptin HCS is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin 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 25 mg, 50 mg or 100 mg of sitagliptin as an active substance. Film-coated tablets are packed in OPA/Alu/PVC//Alu blisters and available as packs of 14, 28, 30, 56, 60, 90 and 98 film-coated tablets in a box.

*Sitagliptin HCS 25 mg film-coated tablets*

Pink, round, slightly biconvex, film coated tablets with engraved mark K25 on one side of the tablet (diameter approx. 7 mm, thickness 2.0 – 3.2 mm).

*Sitagliptin HCS 50 mg film-coated tablets*
Light orange, round, biconvex, film coated tablets with score line on one side of the tablet. Tablet is engraved with mark K on one side of the score line and with mark 50 on the other side of the score line (diameter approx. 9 mm, thickness 2.8 – 3.8 mm).
The tablet can be divided into equal doses.

*Sitagliptin HCS 100 mg film-coated tablets*
Brown orange, round, biconvex, film coated tablets with score line on one side of the tablet. Tablet is engraved with mark K on one side of the score line and with mark 100 on the other side of the score line (diameter approx. 11 mm, thickness 3.3 – 4.5 mm).
The tablet can be divided into equal doses.

The other ingredients are:

*Tablet core*
cellulose, microcrystalline
calcium hydrogen phosphate
croscarmellose sodium
sodium stearyl fumarate
magnesium stearate

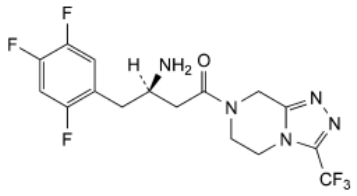
*Film-coating*
Opadry 85F280010 II HP white:
- poly(vinyl alcohol)
- macrogol 3350
- titanium dioxide (E171)
- talc

red iron oxide (E172)
yellow iron oxide (E172)

## II.2 Drug Substance

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.

## II.3 Medicinal Product

Pharmaceutical development

The main aim was to develop an immediate release formulation of sitagliptin, with adequate stability and essentially similar to the reference product Januvia film-coated tablets (Merck Sharp and Dohme B.V.). Formulation development was carried out on the 100 mg strength, as well as 25 mg strength. The composition of the middle 50 mg strength was then translated from the higher and lower strengths. The composition of all strengths is proportionally equivalent. Due to the patent protection, different form of active substance was used in the proposed generic, i.e. sitagliptin base instead of sitagliptin phosphate monohydrate, which is comprised in the reference medicinal product. Consequently, the proposed manufacturing process also differs from the one used for the reference product. The proposed product is manufactured by roller compaction (dry granulation).

Manufacturing

The finished product is manufactured by dry granulation (roller compaction) and a detailed description of the process has been provided in the dossier. In brief, it involves manufacturing of blend for roller compaction, manufacturing of granulate, manufacturing of compression mixture, tabletting and film coating. Process validation was performed on a batch size of 100,000 tablets of each. Process validation scheme to be applied in the commercial manufacture and at every scale-up has been provided.

Specification

The finished product release and shelf-life specifications include appropriate tests and limits for appearance (visual), identification of sitagliptin (HPLC/DAD, in-house), uniformity of dosage units (Ph.Eur.), disintegration (Ph.Eur.), related substances (in-house), content of sitagliptin (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 and accelerated conditions which were packed in OPA/Al/PVC-Al blister as proposed for marketing.
Shelf-life has been approved for 2 years with following storage conditions: Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.

## 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

Pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin are well known. As sitagliptin is widely used, well-known active substance, 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)

Consumption data for sitagliptin in several concerned member states (CMSs) were submitted. According to the presented data the consumption has increased, but not significantly. The applicant has performed statistical analysis of the consumption within the period of 2014-2017. Even though not all CMSs have been included; this approach was accepted.

## 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 consumption data did not indicate that sitagliptin 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 one bioequivalence study, which is discussed below.

## IV.2 Pharmacokinetics

Biowaiver

Applicant submitted bioequivalence study with Sitagliptin HCS 100 mg film-coated tablets and requested biowaiver for additional 25 mg and 50 mg strengths. The pharmacokinetics of sitagliptin is dose proportional in the dosing range. For such, cases a bioequivalence study using the highest strength is recommended.

To fulfil criteria for biowaiver for 25 mg and 50 mg strengths, following criteria have been met:

a) active substance sitagliptin express linear pharmacokinetics over the dose 25 mg – 400 mg,
b) all strengths of Sitagliptin HCS are manufactured by the same manufacturing process,
c) the qualitative composition of the different strengths is the same,
d) the composition of the strengths is quantitatively proportional (the core of the tablet is quantitatively proportional, not the coating),
e) the dissolution profiles of all three strengths were comparable.

Sitagliptin HCS 25 mg and 50 mg film-coated tablets exhibited very rapid dissolution in all investigated media. General biowaiver criteria were fulfilled according to the Guideline on

investigation of bioequivalence. Therefore, the results of the below discussed bioequivalence study with 100 mg strength were extrapolated to the strengths 25 mg and 50 mg.

Bioequivalence study

To support the application, the applicant has submitted as report 1 bioequivalence study 17-562A: single-dose, comparative bioavailability study of two formulations of sitagliptin 100 mg film-coated tablets under fasting conditions. This study was designed as single dose, open label, randomised, two-period, two-treatment, two-sequence cross-over comparative bioavailability study in healthy, non-smoking, male and female subjects under fasting conditions.

Test and reference products

Sitagliptin HCS 100 mg film-coated tablets has been compared to Januvia (sitagliptin) 100 mg film-coated tablets by Merck Sharp & Dohme B.V., the Netherlands.

Population studied

There were 30 subjects planned for inclusion to the bioequivalence study, 30 subjects were enrolled, and 30 subjects completed the study. All the subjects were included in the safety, pharmacokinetic (PK) and statistical analysis.

Analytical methods

Analysis of plasma concentration of sitagliptin was done by a validated LC with MS/MS detection. Good laboratory practice (GLP) statement was included. Bioanalytical analyst was blinded towards the treatments administered to subjects.

Pharmacokinetic variables

Following pharmacokinetics variables were estimated: $C_{max}$, $AUC_t$, $AUC_{inf}$, $T_{max}$, Kel, Thalf, $AUC_t/AUC_{inf}$.
The pharmacokinetic parameters were calculated using a non-compartmental approach in SAS (version 9.4).

Statistical methods

Descriptive statistics for the PK parameters of sitagliptin were calculated. Descriptive statistics included number of observations, arithmetic mean, standard deviation, geometric mean (where applicable), coefficient of variation (CV), median, minimum and maximum. Analysis of variance (ANOVA) (PROC GLM) was performed on log-transformed plasma sitagliptin $AUC_{t,}$ $AUC_{inf}$, and $C_{max}$.
Based on log-transformed data, ratios of the geometric means for treatments and the corresponding 90% confidence intervals (CIs) were calculated for $AUC_t$, $AUC_{inf}$, and $C_{max}$. The 90% CIs of the relative mean plasma sitagliptin $AUC_t$ and $C_{max}$ of the test to reference products should be between 80.00 and 125.00%.

Results

**Table 2–1 Summary of Study Results Based on Plasma Sitagliptin Levels**

| Parameter | Trt | n | Arithmetic Mean (CV%) | Geometric Mean | Contrast | Ratio (%) | 90% Confidence Interval | Intra-Sbj CV(%) |
|---|---|---|---|---|---|---|---|---|
| $C_{max}$ | A | 30 | 394.70 (24) | 384.07 | A vs B | 98.10 | 92.71 - 103.79 | 13 |
| (ng/mL) | B | 30 | 406.63 (28) | 391.52 | | | | |
| $AUC_t$ | A | 30 | 3492.59 (18) | 3441.75 | A vs B | 99.48 | 97.88 - 101.11 | 4 |
| (ng·h/mL) | B | 30 | 3505.52 (16) | 3459.77 | | | | |
| | | n | Median | Range | | | | |
| $T_{max}$ | A | 30 | 2.25 | 0.50- 5.00 | | | | |
| (h) | B | 30 | 2.02 | 0.75- 6.00 | | | | |

Treatment A: tested product Sitagliptin HCS 100 mg
Treatment B: reference product Januvia 100 mg

**$AUC_{0-t}$** 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 products when administered under fasting condition.

90% CI for $AUC_{inf}$ is 98.18-101.90 with Test/Ref Ratio of 100.02.

Safety

The administration of the study medicinal products was generally well tolerated by the healthy subjects participating in this study. Overall, there were 5 adverse effects (AEs) affecting 4 subjects in the study. Two subjects receiving test (hypoglycaemia, dizziness) and 3 subjects receiving reference product (tachycardia, catheter side related reaction, fatigue) reported an AE in their corresponding treatment.

Additional data

Applicant submitted dissolution profiles to compare test and reference medicinal products (batches used in the bioequivalence study) as an addition to the bioequivalence studies. Dissolution profiles were performed in three dissolution media - in 0.1M hydrochloric acid, acetate buffer solution pH 4.5 and phosphate buffer solution pH 6.8.
Both tested formulation express similar dissolution profiles in all three-dissolution media – more than 85% of sitagliptin was dissolved within 15 minutes.

Conclusion on bioequivalence study

Based on the submitted bioequivalence study Sitagliptin HCS 100 mg film-coated tablets (HCS BV, Belgium) is considered bioequivalent with Januvia 100 mg film-coated tablets by Merck Sharp & Dohme B.V., the Netherlands.

## 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 HCS.

- Summary table of safety concerns as approved in RMP

| | |
|---|---|
| Important identified risks | None |
| 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 study it was concluded, that Sitagliptin HCS 100 mg film-coated tablets by HCS BV, Belgium is considered bioequivalent with Januvia 100 mg film-coated tablets by Merck Sharp & Dohme B.V., the Netherlands. Biowaiver for lower strengths 25 mg and 50 mg was accepted.

## V. USER CONSULTATION

The package leaflet 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 English.
The results show that the package leaflet 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

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/0277/001-003/DC.

Reference medicinal product was Januvia, film-coated tablets from Merck Sharp & Dohme B.V., the Netherlands authorised in the European Union via centralised procedure (EMEA/H/C/722) since 21 March 2007.

Based on the results of submitted bioequivalence study it was concluded, that Sitagliptin HCS 100 mg film-coated tablets by HCS BV, Belgium is considered bioequivalent with Januvia 100 mg film-coated tablets by Merck Sharp & Dohme B.V., the Netherlands. Biowaiver for lower strengths 25 mg and 50 mg was accepted.

Quality aspects of the dossier were adequately described; specifications of API sitagliptin were adequately presented in the ASMF and that of finished medicinal product were 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 Januvia film-coated tablets was adequately demonstrated and have, therefore, granted the marketing authorisation. This decentralised procedure was positively concluded on 14 January 2023 (D200).