COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sitagla 25 mg, 50 mg and 100 mg film-coated tablets (sitagliptin hydrochloride monohydrate)

NL License RVG: 128972 - 128974

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This module reflects the scientific discussion for the approval of Sitagla 25 mg, 50 mg and 100 mg film-coated tablets. The procedure was finalised on 13 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
PPARγ	Peroxisome proliferator-activated receptor gamma
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 Sitagla 25 mg, 50 mg and 100 mg film-coated tablets, from Maddox Pharma Swiss B.V.

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

<u>as monotherapy</u>

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

<u>as dual oral therapy in combination with:</u>

- 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.

<u>as triple oral therapy in combination with:</u>

- 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.

The product 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, which concerns a generic application.

In this national procedure, essential similarity is proven between the new product and the innovator product Januvia 25 mg, 50 mg and 100 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/07/383) since 21 March 2007 by Merck Sharp & Dohme B.V. The reference product contains sitagliptin phosphate as active substance, while the new product contains sitagliptin hydrochloride monohydrate salt. Although the generic product is different in the salt form and is not described in any pharmacopoeia, sitagliptin hydrochloride is classified as an identical therapeutically entity according to Article 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." Relevant comparative dissolution, assay and impurity study between the generic products were performed and found acceptable.

II. QUALITY ASPECTS

II.1 Introduction

Sitagla 25 mg, 50 mg and 100 mg are film-coated tablets. The three strengths of the film-coated tablets can be distinguished by the different sizes, colours and debossing and are as follows:

Sitagla 25 mg
The 25 mg strength tablets are pink, film-coated, round of 6.2 ± 0.2 mm in diameter, debossed with '25' on one side. Each tablet contains as active substance sitagliptin hydrochloride monohydrate, equivalent to 25 mg of sitagliptin.

Sitagla 50 mg
The 50 mg strength tablets are light beige, film-coated, round of 8.0 ± 0.2 mm in diameter, debossed with '50' on one side. Each tablet contains as active substance sitagliptin hydrochloride monohydrate, equivalent to 50 mg of sitagliptin.

Sitagla 100 mg
The 100 mg strength tablets are beige, film-coated, round of 9.9 ± 0.2 mm in diameter, debossed with '100' on one side. Each tablet contains as active substance sitagliptin hydrochloride monohydrate, equivalent to 100 mg of sitagliptin.

The excipients are:

Tablet core - microcrystalline cellulose (E460), calcium hydrogen phosphate (341(ii)), sodium starch glycolate (type A) and magnesium stearate (E470b).
Film-coating - polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172) (only 50 mg).

The film-coated capsules are packed in opaque polyvinyl chloride/polyethylene/ polyvinylidene chloride-aluminium (PVC/PE/PVdC-Al) or oriented polyamide (OPA)/Al/PVC-aluminium perforated or not perforated unit blisters.

II.2 Drug Substance

The 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; very slightly soluble in ethanol and practically insoluble in hexane. It has one chiral centre. The R-enantiomer is the active form and used. For this product the same crystalline form is consistently produced, the reproducibility of the manufacturing process in terms of polymorphism has been demonstrated with three validation batches.

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, starting with a starting material, and one chloride-salt forming step. The process has been described in sufficient detail. The starting materials are acceptable. Batch sizes and yields have been indicated. 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. A known nitrosamine impurity is formed and controlled during manufacturing.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the in-house test methods. Batch analytical data demonstrating compliance with this specification have been provided for three batches. The batches comply with the proposed specification.

Stability of drug substance

Stability data on the active substance has been provided for fourteen (ten at site 1 and three at site 2) batches when stored under the conditions described in the corresponding AMSF. Based on the data submitted, the proposed re-test period can be up to 12 months (the period covered by long-term data). However, a re-test period of 60 months is acceptable for this active substance.

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 choices of the packaging and manufacturing process are justified in relation to the innovator product. The manufacture and composition of the 100 mg strength biobatch used in the pivotal bioequivalence study was similar to the proposed marketed product. The requested biowaiver of strength for the two lower strengths can be

accepted from a chemical-pharmaceutical point of view. The dissolution method used for routine dissolution was shown to be discriminatory and is acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production scale batches of each strength at each manufacturing site, in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph. Eur. requirements. For the coating mixtures, in-house specifications are defined. These 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 the active substance, dimensions, water content, disintegration, average weight, uniformity of dosage units (content uniformity), dissolution, 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. Consistency of the polymorphic form in the drug substance and over manufacture and storage of the drug product is considered sufficiently justified. Hence, further control of the polymorphic form in the final product specifications is not deemed necessary. Also, other limit values are considered to be acceptable.

An updated risk assessment report for nitrosamines has been provided based on EMA/409815/202 Rev 10. All potential sources have been evaluated. Based on the potential presence of intermediate and degradation impurities in water and excipient cellulose microcryst and sodium starch glycolate, there is a high risk of formation of a nitrosamine. Results of confirmatory testing have been provided. Based on the results, it was decided to apply routine testing for the nitrosamine in sitagliptin tablets. This will be incorporated in the product specification.
Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from six production scale batches of each strength (three from each manufacturing 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 production scale batches of each strength from each manufacturing site stored at 25°C/ 60% RH (27 months) (real-time) and 30°C/70% RH (6 months) (accelerated) in accordance with applicable European guidelines. 18 to 24 months of real-time (25°C/60% RH) and 6 months accelerated (40°C/75% RH) data are available of studies where a nitrosamine impurity has not been tested. Instead results of the impurity are available of testing recent batches at t=0 and of six batches stored for 27 months at 25°C/60%RH and 30°C/7%RH. A slight increase in the impurity is observed at 25°C/60%RH and a higher increase at 30°C/70%RH. The impurity level remains below the shelf-life limit and

is consistent when stored according to its storage conditions. Photostability studies were performed in accordance with ICH Q1B. No significant change in the tested parameters were observed in the directly exposed product, it was concluded that the tablets are not sensitive to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are “Do not store above 30°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 Sitagla 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 Sitagla 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 Januvia 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 hydrochloride monohydrate is a well-known active substance 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a pivotal bioequivalence study in which the pharmacokinetic profile of the test product Sitagla 100 mg (Maddox Pharma Swiss B.V., Netherlands) was compared with the pharmacokinetic profile of the reference product Januvia 100 mg (Merck Sharp & Dohme B.V., Netherlands). A pilot study was also performed.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. Comparative dissolution has been demonstrated at pH 1.2, 4.5 and 6.8. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

A bioequivalence study on the highest strength (100 mg strength) has been carried out. Pharmacokinetics are linear in the therapeutic dose range. A biowaiver is requested for the 25 mg and 50 mg strength as all the following criteria are fulfilled:

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open-label, balanced bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-42 years. Each subject received a single dose (1 x 100 mg tablet) of one of the two sitagliptin hydrochloride monohydrate formulations. The tablet was orally administered with 240 mL water after an overnight fasting period. Blood glucose was monitored during the study and a number of subjects were found to have a blood glucose level ≤ 85 mg/ dL and were therefore administered 20% glucose solution in water. There were three dosing groups, which were dosed with a two day gap between group. There were two dosing periods, separated by a washout period of five days. The differences between the three dosing groups were determined to be statistically non-significant.

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, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. Since co-administration of a high-fat meal with sitagliptin has no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

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
40 subjects participated in the study and all were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin hydrochloride monohydrate, 100 mg under fasted conditions.

Treatment N=40	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	4800 ± 980	4902 ± 990	586 ± 155	2.14 (0.67 – 5.50)
Reference	4928 ± 1118	5031 ± 1133	604 ± 197	2.38 (1.0 – 5.0)
***Ratio (90% CI)**	0.98 (0.96 – 1.00)	-	0.98 (0.91 – 1.06)	-

$AUC_{0-\infty}$	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 study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Sitagla 100 mg is considered bioequivalent with Januvia 100 mg.

The results of study with 100 mg formulation can be extrapolated to other strengths 25 mg and 50 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Sitagla.

Table 2. 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

The MEB 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 Januvia. 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

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 test consisted of: a pilot test with four 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

Sitagla 25 mg, 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Januvia 25 mg, 50 mg and 100 mg film-coated tablets 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 Sitagla with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 13 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
1009879	**Type IAin: B.II.b.2.c.1** *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.
1015052	**Type IB: B.II.d.2.d** *Change in control of the Finished Product*	No	14-06-2023	Approved	N.A.
1015012	**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	24-06-2023	Approved	N.A.
1039600	**Type IA: B.I.c.z** *Change in container closure system of the active substance* **Type IA: A.4** *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 excipient (where specified in the technical dossier)*	No	20-09-2023	Approved	N.A.
1066044	**Type II: B.II.d.1.e** *Change in the specification parameters and/or limits of the finished product* • *Change outside the approved specifications limits range*	No	21-03-2024	Approved	N.A.

1068524	**Type IB: B.II.b.1.e** *Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product* • *Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.*	Yes	02-04-2024	Approved	N.A.