COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5415/001-003/DC

Date: 25 August 2022

This module reflects the scientific discussion for the approval of Sitagliptine Auro 25 mg, 50 mg and 100 mg, film-coated tablets. The procedure was finalised on 19 May 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 Sitagliptine Auro 25 mg, 50 mg and 100 mg, film-coated tablets, from Aurobindo Pharma B.V.

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

This 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Januvia 25 mg, 50 mg and 100 mg film-coated tablets which have been registered in the EEA by Merck Sharp & Dohme B.V. since 21 March 2007 via a centralised procedure (EMEA/H/C/000722).

The concerned member states (CMS) involved in this procedure were Denmark and Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Sitagliptine Auro 25 mg, 50 mg and 100 mg are film-coated tablets, packed in white opaque PVC/PVdC/-Al blisters or white opaque HDPE containers closed with a white opaque polypropylene closure.

- The 25 mg strength is a pink coloured, round shaped, biconvex, film-coated tablet debossed with 'SG' on one side and '25' on the other side, with a diameter of about 6.2 mm.
- The 50 mg strength is a light beige coloured, round shaped, biconvex, film-coated tablet debossed with 'SG' on one side and '50' on the other side, with a diameter of about 8mm.
- The 100 mg strength is a beige coloured, round shaped, biconvex, film-coated tablet debossed with 'SG' on one side and '100' on the other side, with a diameter of about 9.9 mm.

The excipients are:
Tablet core - microcrystalline cellulose (grade-102), calcium hydrogen phosphate, croscarmellose sodium, sodium stearyl fumarate and magnesium stearate.
Film-coating - poly(vinyl) alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), yellow iron oxide (E172) and red iron oxide (E172).

The tablet cores of the different strengths are qualitatively the same and quantitatively proportional.

II.2 Drug Substance

The active substance is sitagliptin hydrochloride monohydrate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). Sitagliptin hydrochloride monohydrate is a white or almost white powder and is freely soluble in water. The active substance shows polymorphism and is consistently manufactured as the same polymorphic form (monohydrate), which is controlled as part of the drug substance specification. Sitagliptin has one asymmetric carbon in its molecular structure and is enantiopure.
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 of sitagliptin hydrochloride monohydrate, is a synthetic process with two starting materials. The synthesis consist of five chemical transformation with five isolated intermediates, followed by a final purification step with an organic solvent. The synthesis starts with the first starting material, the second starting material is introduced in the fourth step of the synthesis. The final active substance is compacted. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is established in-house by the MAH, based on the specification as described in the ASMF, with additional requirements for particle size and bulk density. The specification includes tests for description, solubility, identification, chlorides, assay, water, sulphated ash, sitagliptin enantiomer, related substances, residuals of solvents and any unspecified impurity, and microbiological quality. The proposed specifications are acceptable. Furthermore, the analytical methods have been adequately described and validated. Batch analytical data demonstrating compliance with the drug substance specification have been submitted for four full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for four production scaled batches in accordance with applicable European guidelines (ICH stability guidelines). The batches were stored at 25°C/60% RH (6 months) and 40°C/75% RH (6 months). The following parameters were investigated: description, identification, water, assay, related substances, sitagliptin enantiomer, microbiological quality and solubility. The stability data show no clear trends or changes in any of the tested parameters at both storage conditions. All results were within the specification limits. Based on the submitted stability data, a shelf life of 6 months was granted. Although no storage precautions are needed based on the available stability data, there is no objection against the proposed storage condition ‘Store in a well closed container, at controlled room temperature’.

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 choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the reference products, selection of the manufacturing method, performance of formulation optimisation studies, dissolution method development and performance of comparative dissolution studies. A bioequivalence study was performed with the 100 mg product strength versus the respective reference product strength. For the additional 25 mg and 50 mg strengths a biowaiver was claimed. The test batch used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process at a representative scale. Comparative dissolution testing at three pH’s has been successfully studied complementary to the bioequivalence study and in

support of the biowaiver for the additional strengths. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are the blending and lubrication of the tablet core excipients, compression, coating and packaging. The different product strengths are manufactured from the same common blend. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scaled batches per strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The tablet core excipients comply with Ph.Eur. (tablet core excipients) or in-house (ready to use coating materials) requirements, with additional control of functionality related characteristics where relevant. 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 description, identification (of drug substance and colourants), dissolution, average mass, uniformity of dosage units, assay, related substances, water, N-Nitroso triazolopyrazine and microbial contamination. The release and shelf-life requirements/limits are identical, except for water content. The proposed specification is acceptable. Furthermore, the analytical methods have been adequately described and validated. Batch analytical data from three pilot scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches per strength in accordance with applicable European guidelines (ICH stability guidelines). The batches were stored in PVC/PVdC-Al blisters and HDPE containers at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The following parameters were investigated: description, assay, dissolution, water, microbial contamination and related substances. Except for a slight increase observed in water content at 40°C/75% RH, no trends or changes were observed in any of the tested parameters at both storage conditions and in any of the packaging configurations. Levels of N-Nitroso triazolopyrazine were determined on the stability batches 23 months after the manufacture date. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Based on the submitted stability data, a shelf life of 24 months was granted. This medicinal product does not require any special storage conditions.

In-use stability data have been provided for two 25 mg batches packed in 500's count HDPE container and two 100 mg batches packed in 1000's count HDPE container stored at 25°C/60% RH (3 months). In-use was simulated by opening the bottles daily for at least one

minute and then replacing the cap. No trends or changes were observed in any of the tested parameters (description, assay, dissolution, water, microbial contamination and related substances) and all results were within the specification limits. In-use stability was adequately investigated in the worst-case HDPE bottle configuration. In line with the EMA Q&A's on in-use stability studies for multi-dose containers, there is no need to claim or lay down an in-use shelf-life for the product.

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 Sitagliptine Auro 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 Sitagliptine Auro 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 member states 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 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sitagliptine Auro 100 mg, film-coated tablets (Aurobindo Pharma B.V, The Netherlands) is compared with the pharmacokinetic profile of the reference product Januvia 100 mg filmcoated 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 EU reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

Based on acceptable bioequivalence study with the 100 mg product strength, a bio-waiver was requested for the 50 mg and 100 mg strength. A biowaiver can be granted based if the following criteria are met:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the composition of the strengths are quantitatively proportional
- similarity in in vitro dissolution profiles, i.e. all additional strengths show very rapid dissolution, >85% in 15 min, at all three pH levels of 1.2, 4.5 and 6.8 using paddle apparatus at 50 rpm.

The comparative dissolution testing was assessed. The reference and tests batches used in the bioequivalence study were also use for the dissolution testing. The submitted data demonstrated that: the batch used in the bioequivalence study and dissolution testing was manufactured according to the finalised composition and manufacturing process at a representative scale, the results of the bioequivalence study show a correlation dose-plasma concentrations (AUC0-∞), the qualitative composition of the three strengths is the same, and the dissolution profiles of the 25 mg and 50 mg, tested at three tested pH's, was similar to the 100 mg strength. Based on the submitted information and in vitro data, it has been demonstrated that the criteria described above was met and a biowaiver has been granted.

Bioequivalence study

Design

A single-dose, open-label, randomised, two-period, two-treatment, two-sequence, crossover, oral bioequivalence study was carried out under fasted conditions in 36 healthy, adult, human male subjects, aged from 20-43 years a body mass index (BMI) in the range of 18.76-29.94 kg/m^2. Each subject received a single oral dose (100 mg) of sitagliptin hydrochloride monohydrate of the test product or reference product. The tablet was orally administered after overnight fasting of at least 10 hours. The subjects were in sitting posture at the time of dosing and instructed not to crush or chew the study drug and consume it as a whole along with given 240 mL of 20% glucose solution at room temperature in both periods. Oral cavity check was performed. Drinking water restriction was maintained one hour before dosing and until one hour post dose and all the subjects were refrained from taking water during this period. Subjects were given 60 mL of 20% glucose solution at every hour up to 4 hours after dosing in both periods. Subjects were instructed to remain seated or ambulatory for first 2 hours following drug administration. Pre study, all subjects were provided with a 1054 Kcal dinner on the day of check-in during each period. The meal on day 1 and day 2 is as described in Table 1, identically in both periods for all the subjects.

Table 1. Meal plan day 1 and day 2.

Meal plan				
Meal type	**Day-1 (approx. 2482 kcal)**		**Day-2 (approx. 2469 kcal)**	
	Approx. calories	**Schedule time (hr)**	**Approx. calories**	**Schedule time (hr)**
Breakfast	NA	NA	402 Kcal	24.00 post-dose
Lunch	1066 Kcal	4.00 post-dose	905 Kcal	28.00 post-dose
Snacks	408 Kcal	8.00 post-dose	235 Kcal	32.00 post-dose
Dinner	1008 Kcal	13.00 post-dose	927 Kcal	36.00 post-dose

Provided meal was completely consumed by all subjects in both periods.

There were two dosing periods, separated by a washout period of eight days.

Two pre-dose blood samples were collected in each period at 0.00. Blood samples were collected in each period at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after administration of the products.

The design of the study is acceptable. Dosing under fasting conditions is justified as the immediate release formulation can be taken 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

Two subjects were absent in period II. Therefore, 34 subjects completed the study and were eligible for pharmacokinetic analysis. The results are described in Table 2.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin hydrochloride monohydrate, under fasted conditions.

Treatment N=34	AUC_{0-t} (g/mL/h)	$AUC_{0-\infty}$ (g/mL/h)	C_{max} (g/mL/h)	t_{max} (h)	$t_{1/2}$ (h)
Test	4849.9 ± 637.4	4959.8 ± 670.7	506.0 ± 85.3	2.33 (1.33 – 6.00)	8.8 ± 1.27
Reference	4477.4 ± 717.1	4583.3 ± 747.6	473.9 ± 92.4	2.33 (1.00 – 5.00)	9.0 ± 1.23
***Ratio (90% CI)**	1.09 (1.06 – 1.12)	--	1.07 (1.03-1.12)	--	--
CV (%)	6.6	--	10.7	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Sitagliptine Auro 100 mg film-coated tablets are considered bioequivalent with Januvia 100 mg film-coated tablets. Furthermore, the results of the bioequivalence study with the 100 mg formulation can be extrapolated to the other strengths, 25 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 Sitagliptine Auro.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• Pancreatic cancer
Missing information	• Exposure during pregnancy and during 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 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

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 Januvia 25 mg, 50 mg, 100 mg film-coated tablets (EMEA/H/C/000722) for content and to Mebevirine HCL Aurobindo 200 mg modified-release capsules, hard (NL/H/3750/001/DC) for design and layout. 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

Sitagliptine Auro 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 filmcoated tablets. Januvia 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sitagliptine Auro with the

reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 May 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