COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sitagliptin STADA 25 mg, 50 mg and 100 mg film-coated tablets
(sitagliptin hydrochloride)

NL/H/4938/001-003/DC

Date: 17 January 2022

This module reflects the scientific discussion for the approval of Sitagliptin STADA 25 mg, 50 mg and 100 mg film-coated tablets. The procedure was finalised at 8 September 2021. 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
PPARy	Proliferator-activated receptor gamma
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 Sitagliptin STADA 25 mg, 50 mg and 100 mg film-coated tablets, from Stada Arzneimittel AG.

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.

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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Januvia 25 mg, 50 mg and 100 mg film-coated tablets which has been authorised in the EU in 2007 with marketing authorisation numbers EU/1/07/383/001-0024.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Sitagliptin STADA 25 mg
Round-shaped, biconvex, film-coated tablets, pink, debossed with "LC" on one side.

Sitagliptin STADA 50 mg
Round-shaped, biconvex, film-coated tablets, orange, debossed with "C" on one side.

Sitagliptin STADA 100 mg
Round-shaped, biconvex, film-coated tablets, beige, debossed with "L" on one side.

The product contains as active substance either 25 mg, 50 mg or 100 mg of sitagliptin hydrochloride equivalent to 25 mg, 50 mg or 100 mg sitagliptin respectively.

The film-coated tablets are packed in PCV/PVDC/aluminium blisters or HDPE bottles with a polypropylene screw-cap.

The excipients are:
All strengths
Tablet core - calcium hydrogen phosphate (E341), cellulose microcrystalline (E460), croscarmellose sodium (E468), sodium stearyl fumarate and magnesium stearate (E470b).

Sitagliptin STADA 25 mg
Film coating - lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin (E1518) and iron oxide red (E172).

Sitagliptin STADA 50 mg and 100 mg
Film coating - polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol/PEG (E1521), talc (E553b), iron oxide yellow (E172)and iron oxide red (E172).

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is sitagliptin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Sitagliptin hydrochloride is a white or almost white powder. It is freely soluble in water. The drug substance has one chiral centre: the amino-group is in the R-configuration: (3R)-3-amino. The substance is not hygroscopic. Several polymorphic forms exist. Both drug substance suppliers manufacture the same polymorphic form of the drug substance, referred to as form I.

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

Two different manufacturers are used to produce sitagliptin hydrochloride, named manufacturer I and II.

Manufacturer I

Manufacturer I uses nine chemical synthesis steps to synthesize sitagliptin hydrochloride after which it is milled, sieved and packed. The choice of the regulatory starting materials is justified. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Manufacturer II

Manufacturer II uses eight chemical synthesis steps to synthesize sitagliptin hydrochloride after which it is dried, milled, sifted and packaged. The choice of the regulatory starting materials is justified. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The MAH's drug substance specification contains tests for description, identification, hydrochloric acid content, water content, residue on ignition, enantiomeric impurity, related substances, assay, residual solvents and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for four batches from manufacturer I and two batches from manufacturer II.

Stability of drug substance

Manufacturer I

Stability data on three production scaled batches have been provided stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. The batches were stored in double LDPE bags (inner white, outer black) in a HDPE container. There are no clear trends to be observed in the results of the test parameters. Results of a photostability study in accordance with ICH Q1B showed that the drug substance is not sensitive to light. Based on these results, the proposed retest period (three years) and the storage conditions (no special storage conditions) are acceptable.

Manufacturer II

Stability data on seven production scaled batches (including one micronized batch) have been provided stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. All results complied with the specification. A slight decrease in assay is observed at long-term conditions. No changes in impurity levels were seen (below detection level). Based on these results, the proposed retest period (24 months) and the storage conditions (Store in an air tight container under nitrogen at a temperature up to 25°C) are acceptable.

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 biobatch used in the bioequivalence studies was similar to the proposed marketed product. For the two lower strengths a biowaiver of additional strengths is requested and considered to be acceptable. The development of the product has been adequately performed.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for at least three commercial-scale batches of all strengths from each drug product manufacturing site.

Control of excipients

The excipients comply with the Ph. Eur. requirements, with additional control of functionality-related characteristics where relevant. For the ready-to use film-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 description, identification, water content, uniformity of dosage units (content uniformity), dissolution, related substances, assay and microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Except for the test for water content, the release and shelf-life requirements are identical. The specification is acceptable. An adequate nitrosamines risk evaluation has been provided, concluding absence of risk.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed manufacturing sites have been provided for at least three pilot scaled batches per strength from both manufacturing sites, demonstrating compliance with the current release specification.

Stability of drug product

Stability data on the product has been provided for at least three production scaled batches per strength from both manufacturing sites stored at 25°C/60% RH (up to 18 months) and 40°C/75% RH (six months) accordance with applicable European guidelines demonstrating the stability of the product for 24 months in the packaging intended for marketing. No clear trends or changes were seen in any of the tested parameters, irrespective of the storage condition, packaging configuration, manufacturing site or product strength. All results comply with the specification. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months without any special storage conditions is justified for both packaging configurations.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose monohydrate and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sitagliptin STADA 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 Sitagliptin STADA 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 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 Sitagliptin 100 mg tablets (Laboratorios Liconsa, S.A., Spain) is compared with the pharmacokinetic profile of the reference product Januvia 100 mg film-coated tablets (Merck Sharp & Dohme Ltd.) from the Spanish market.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution with the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH requested a biowaiver for the lower strengths (25 mg and 50 mg) of the product based on the bioequivalence study with the 100 mg formulation.

The following criteria from CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** have to be met for a biowaiver of strengths:

a. The pharmaceutical products are manufactured at the same site by the same manufacturer and manufacturing process.
b. Linear pharmacokinetics, i.e. proportional increase in AUC and Cmax with increased dose, over the therapeutic dose range.
c. The qualitative composition of the different strengths is the same.
d. The composition of the strengths is 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, colour agents and flavours are not required to follow this rule).
e. Appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing

It was concluded that the qualitative and quantitative composition of the different strengths are dose proportional, all strengths are manufactured by the same process and that the dissolution profiles are similar. Therefore, the criteria for a biowaiver of strengths were met and the biowaiver was granted for the lower strengths.

Bioequivalence studies

Design

This was an open label, balanced, randomised, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study and was carried out under fasted conditions in 38 healthy adult subjects, aged 20-44 years. Each subject received a single dose (100 mg) of either the test or reference sitagliptin hydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at pre-dose (0.000 hour) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 18.0, 24.0, 36.0, 48.0 and 72.0 hours following drug administration in each period.

Sitagliptin hydrochloride may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sitagliptin hydrochloride. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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.

The design of the study is acceptable.

Results

Out of a total of 38 subjects, 32 subjects were eligible for pharmacokinetic analysis. Four subjects were withdrawn from the study because of adverse events (vomiting, upper respiratory tract infection and hyperchlorhydria). Two other subjects were withdrawn from the study due to wrong administration of investigation medicinal product in period two.

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

Treatment N=32	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	4406.3 (± 816.9)	4467.8 (± 816.8)	501.7 (± 137.4)	3.0 (0.75 to 5.0)
Reference	4362.6 (± 873.1)	4430.7 (± 877.6)	503.7 (± 141.3)	3.0 (0.75 to 5.0)
***Ratio (90% CI)**	1.011 (0.9971 – 1.0248)	--	1.002 (0.9463 – 1.0602)	--

$AUC_{0-\infty}$ 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

**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 Sitagliptin STADA is considered bioequivalent with Januvia.

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 Sitagliptin STADA.

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 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

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 language used for the purpose of user testing the PL was English. The test consisted of a pilot test 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

Sitagliptin STADA 25 mg, 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Januvia. 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sitagliptin STADA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 September 2021.

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