COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sitagliptine Amarox 25 mg, 50 mg, 100 mg film-coated tablets

(sitagliptin hydrochloride)

NL/H/4248/001-003/DC

Date: 3 September 2019

This module reflects the scientific discussion for the approval of Sitagliptine Amarox. The procedure was finalised at 21 February 2019. 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
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 Amarox 25 mg, 50 mg, 100 mg film-coated tablets from Hetero Europe S.L.

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

Sitagliptine Amarox 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, 50 and 100 mg film-coated tablets (EU/1/07/383) which has been centrally registered in EEA by Merck Sharp & Dohme Ltd. since 21 March 2007.

The concerned member state (CMS) involved in this procedure was Germany and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Sitagliptine Amarox is a round, pink film-coated tablet which is available in three strengths:

- 25 mg film-coated tablets are debossed with “S17” on one side and “H” on the other side.
- 50 mg film-coated tablets are debossed with “S16” on one side and “H” on the other side.
- 100 mg film-coated tablets are debossed with “S15” on one side and “H” on the other side.

And contains as active substance 25 mg, 50 mg, or 100 mg of sitagliptin, as 27.238 mg, 54.476 mg or 108.952 mg of sitagliptin hydrochloride.

The film-coated tablets are packed in transparent PVC/PE/PVdC-Aluminium blister packs and HDPE container with polypropylene cap.

The excipients are:
Tablet core - microcrystalline cellulose (E460), calcium hydrogen phosphate, anhydrous (E341), croscarmellose sodium (E468), magnesium stearate (E470b), and sodium stearyl fumarate.
Film-coating - Opadry II Pink 85F540099 (25mg, 100mg) and Opadry II Pink 85F540265 (50mg) contain - polyvinyl alcohol-part hydrolysed (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b), iron oxide red (E172), and iron oxide yellow (E172).

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is sitagliptin hydrochloride monohydrate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.), but a monograph is available for sitagliptin phosphate monohydrate. Sitagliptine hydrochloride is a white to off-white powder. It is freely soluble in water. It has one chiral centre. The substance is not hygroscopic. The manufacturer consistently produces polymorph crystalline form III.

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 has been adequately described. It is based on the condensation of two larger blocks. One of these blocks is an intermediate. There are two manufacturers and two manufacturing routes for this intermediate. Three (manufacturer-I) or two (manufacturer-II) additional chemical steps are used to produce the intermediate. Full descriptions of the steps are adequately provided as well as process flow charts.

In the manufacture of a specified starting material, five genotoxic reagents are used or genotoxic intermediates are applicable. Impurities having a structural alert for genotoxicity are adequately dealt with. The reagents are all used or arising in the manufacturing process of the starting material, and all are below acceptable limits.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The results of a six months accelerated and a 24 months long-term stability study are provided for three batches. There are no clear trends to be observed in the results of the test parameters. Based on the data submitted, a retest period could be granted of 36 months. This drug substance product does not require any special storage temperature conditions.

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 choices of the packaging and manufacturing process are justified in relation to the innovator product. The manufacture and composition of the bio-batch used in the bioequivalence studies was similar to the proposed marketed product.

The dissolution method used for routine dissolution was shown to be discriminatory. The arguments as provided by the MAH, supported by the various dissolution results and performed bootstrap analysis, are accepted.
Pharmaceutical development has been adequately performed.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot-scale scale batches of each strength batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. requirements. For the Opadry 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, water content, average mass, uniformity of dosage units, related substances, dissolution, 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.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three pilot-scale scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. All stability results were within specifications. No significant changes were observed in the accelerated stability studies. On basis of the data submitted, a shelf life was granted of two years, without special storage conditions.

One batch of each strength was exposed to UV radiation & visible radiation. Based on the results it is concluded that the drug product is photo-stable and no special storage conditions are required for the finished product.

Stability data for each strength have been provided demonstrating that the product remains stable for one months following first opening of the container.

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 Amarox 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 Amarox 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 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 Amarox 100 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Januvia 100 mg film-coated tablets (Merck Sharp & Dohme Ltd, United Kingdom).

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

Biowaiver

A biowaiver for additional studies was requested for the 25 mg and 50 mg tablets. The MAH fulfilled the general biowaiver criteria from the guideline on the investigation of bioequivalence:

- 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, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths.
- *In vitro* dissolution data between the 25 mg, 50 mg and 100 mg biobatch at a pH of 1.2, 4.5 and 6.8 showing comparable dissolution have been submitted.

The biowaiver for the 25 and 50 mg tablets can be granted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 18-43 years. Each subject received a single dose (100 mg) of one of the 2 sitagliptin formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

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

Three subjects were withdrawn from the study:

- One subject was withdrawn from the study due to an adverse event after dosing in Period I.
- One subject was found positive in alcohol breath test during admission of Period II.
- One subject had taken one cup of tea in the morning on the day before dosing in Period II, hence withdrawn from the study during admission of Period II.

Therefore, 29 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=29	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	4553 ± 1010	493 ± 113	2.67 (0.67 - 5.0)
Reference	4483 ± 814	510 ± 159	2.33 (0.67 - 5.0)
***Ratio (90% CI)**	1.01 (0.98 - 1.04)	0.98 (0.92 - 1.04)	--
CV (%)	6.7	13.8	--

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
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 Sitagliptin Hetero 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 Hetero.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity reaction including anaphylactic reaction, angioedema, rash, urticarial, cutaneous vasculitis, skin exfoliation, Stevens-Johnson Syndrome • Hypoglycaemia with concomitant sulphonylurea • Hypoglycaemia with concomitant insulin • Gastrointestinal disorders, including nausea,

	constipation, diarrhoea, upper abdominal pain, flatulence and related terms (dyspepsia, gastritis and abdominal pain) • Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (ex. Arthralgia, myalgia, myopathy) • Pancreatitis
Important potential risks	• Infections: upper respiratory tract infection, nasopharyngitis, and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis) • Neurotoxicity: tremor, ataxia and balance disorder • Suicidal ideation suicide and depression • Skin reactions: contact dermatitis • Impaired renal function, including acute renal failure (sometimes requiring dialysis) • Pancreatic cancer • Rhabdomyolysis
Missing information	• Patients below 18 years of age • Exposure during pregnancy and lactation • Theoretic carcinogenic potential

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 (EMEA/H/C/000722) regarding the content of the leaflet. Regarding the lay out reference is made to the user test and report of Levetiracetam Hetero. The layout, font size and PL dimension are comparable for both package leaflets. The bridging reports submitted by the MAH have been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sitagliptine Amarox 25 mg, 50 mg, 100 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Januvia 25 mg, 50 mg, 100 mg film-coated 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 Sitagliptin Hetero with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 February 2019.

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