COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Saxagliptine Sandoz 2.5 mg and 5 mg film-coated tablets

(saxagliptin)

NL/H/4425/001-002/DC

Date: 31 July 2019

This module reflects the scientific discussion for the approval of Saxagliptine Sandoz 2.5 mg and 5 mg film-coated tablets. The procedure was finalised on 3 May 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
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 Saxagliptine Sandoz 2.5 mg and 5 mg film-coated tablets from Sandoz B.V.

The product is indicated in adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- as monotherapy when metformin is inappropriate due to intolerance or contraindications
- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 of the SmPC for available data on different combinations).

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 Onglyza 2.5 mg and 5 mg film-coated tablets, which is registered in the EEA by AstraZeneca AB through a centralised procedure (EMEA/H/C/001039). The marketing authorization for Onglyza was granted on 1 October 2009.

The concerned member states (CMS) involved in this procedure were Belgium, Estonia, France, Germany, Slovenia 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

Saxagliptine Sandoz 2.5 mg is a light yellow, round, biconvex film-coated tablet with “SG” embossed on one side and “2.5” on the other side. Each film-coated tablet contains 2.5 mg saxagliptin (as hydrochloride).
Saxagliptine Sandoz 5 mg is a light pink, round, biconvex film-coated tablet with “SG” embossed on one side and “5.0” on the other side. Each film-coated tablet contains 5 mg saxagliptin (as hydrochloride).

The film-coated tablets are packed in OPA/Alu/PVC//Alu/PVC blisters.

The excipients are:

tablet core - lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate

film-coating - hypromellose 2910, macrogol 6000, lactose anhydrous, titanium dioxide (E171), iron oxide yellow (E172) (2.5 mg tablet only), iron oxide red (5 mg tablet only).

Except for the amount of active substance and the colourants (ferric oxide yellow/red and titanium dioxide), the quantitative composition of the two strengths is identical.

II.2 Drug Substance

The active substance is saxagliptin hydrochloride (dihydrate), an established active substance not described in the European Pharmacopoeia (Ph.Eur.). Saxagliptin hydrochloride (dihydrate) is a white to off-white crystalline powder, which is highly soluble in water and buffer over a wide pH range but practically insoluble in ethyl acetate. Saxagliptin contains four chiral centers (stereocenters). Therefore it exhibits stereoisomerism. In addition, the drug substance exists in different crystalline polymorphs. The substance used is monohydrochloride dihydrate, form H2-1.

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 synthesis route for saxagliptin hydrochloride (dihydrate) consists of 5 chemical steps, comprising 3 isolated and 2 non-isolated intermediates followed by 1 final crystallization. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents. The syntheses descriptions of is described in sufficient detail.

Quality control of drug substance

The drug substance specification is established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. The analytical procedures have been described in sufficient detail and are adequately validated. Batch analytical data demonstrating compliance with the drug substance specification have been provided for eight full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months).

Storage under long-term and accelerated conditions showed no upward or downward trends, all results remain within specification up to 60 months. Based on the stability data provided, the claimed re-test period of 60 months with no specific storage conditions has been granted.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, formulation development, dissolution method development, manufacturing process development and the performance of comparative dissolution studies complementary to the bioequivalence study with the 5 mg strength. Similarity of the dissolution results and profiles of the bioequivalence test product strength (5 mg) versus other strength test product (2.5 mg) has been demonstrated in 0.1M HCl (QC medium), acetate buffer pH 4.5 and phosphate buffer pH 6.8. The biowaiver for the 2.5 mg additional strength can be granted from a chemical-pharmaceutical point of view.

Manufacturing process

The manufacturing processes of the finished product consists of blending, compression, film coating and packaging of the product. The manufacturing process is a non-standard process. Validation has been performed on three commercial- scale batches. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients

All excipients comply with the Ph. Eur. or National Formulary, except for 0.1 M HCl. For HCl a description of the analytical methods has been provided. The specifications and control of the excipients are acceptable.

Quality control of drug product

The product specification includes tests for appearance, color, identification of saxagliptin, identification of pigment, water activity, assay of saxagliptin, uniformity of dosage units (content uniformity), related substances, dissolution and microbiological quality.
The release and shelf-life requirements/limits are acceptable. The analytical methods have been adequately described and validated. Batch analysis has been adequately performed on three full-scale batches per strength.

Stability of drug product

Stability information from accelerated (40±2°C/75 ± 5% RH, up to 6 months), intermediate (30 ± 2°C/65 ± 5% RH, up to 12 months) and long term (25 ± 2°C/60 ± 5% RH, up to 24 months) conditions has been provided on four batches of both strengths packaged in the container closure systems proposed for marketing (Al/Al blisters). The conditions used in the stability studies are according to the ICH stability guideline.
Out of specification results were observed at accelerated conditions. However, results at intermediate (30°C/75%RH) and long term 25°C/60%RH) storage conditions were below the

specification limits. The drug product was shown to be photostable. No storage condition related to light sensitivity is required.
Additionally, results of testing dissolution at specification time point 15 minutes have been provided of one batch per strength, demonstrating compliance with the dissolution specification. Based on the results provided, the proposed shelf-life and storage condition have been granted: 24 months, stored in OPA-Al-PVC/Al-PVC blisters, not above 30°C, 'store in the original packaging to protect from moisture'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. Magnesium stearate is of vegetable origin. Lactose is sourced from healthy cows in the same conditions as milk collected for human consumption. TSE statements from the manufacturers of lactose have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Saxagliptine Sandoz 2.5 mg and 5 mg film-coated tablets have 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 Saxagliptine Sandoz 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 Onglyza, 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

Saxagliptin 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Saxagliptine Sandoz 5 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products Onglyza 5 mg (AstraZeneca AB, Sweden) and Onglyza 5 mg (AstraZeneca Canada Inc).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.
The choice of the reference product in the bioequivalence study has been justified, as it has been authorised through a centralised procedure. As only the Swedish reference product is representative for the European market, the data on the Canadian reference product have not been assessed.

Biowaiver
For the 2.5 mg strength a biowaiver has been granted. Oral saxagliptin exhibits linear pharmacokinetics, with exposure to saxagliptin and its major metabolite (5-hydroxysaxagliptin) dose proportional over a dose range of 2.5 - 400 mg administered o.d. for 14 days. The products are manufactured by the same manufacturer, using the same process, the products are dose proportional with a small deviation in accordance with condition c i and ii as described in the guideline. The dissolution profiles are sufficiently comparable.

Bioequivalence studies
Design
A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy subjects (14 males, 26 females), aged 19-53 years. Each subject received a single dose (5 mg) of one of the 3 saxagliptine formulations. The tablet was orally administered after an overnight fast of at least 10 hours. There were 3 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours after administration of the products.

The design is acceptable. The wash-out of 7 days is long enough (half-live is ~3 hours and the wash out is >5 half-lives). The sampling period is long enough, and the sampling scheme is adequate to estimate PK parameters. A single dose, crossover study to assess bioequivalence is considered adequate. Fasting conditions has been applied, which is in accordance with the SmPC.

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
A total of 39 subjects finished the study. One subject discontinued the study due to personal reasons (subject received only the two reference formulations, and no test product).

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

Treatment N=39	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	109 ± 29	110 ± 30	33 ± 10	0.6 (0.3-2.0)	3.5 ± 1.4
Reference	111 ± 30	113 ± 32	32 ± 9	0.8 (0.3-1.4)	3.5 ± 0.9
***Ratio (90% CI)**	0.98 (0.95-1.01)	--	1.04 (0.98-1.10)	--	--
CV (%)	8.4	--	16.1	--	--

$AUC_{0-\infty}$ 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 Saxagliptine Sandoz is considered bioequivalent with Onglyza 5 mg film-coated tablets

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).

Safety
No serious adverse events and no deaths were reported for any of the subjects enrolled in this study. No subject was withdrawn by the investigator for safety reasons. A total of 53 adverse events were reported by 14 (35%) of the 40 subjects who participated in this study. Of these events, 19 occurred after administration of the test, 19 after administration of the Canadian reference product, and 15 after administration of the Swedish reference product. Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

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 Saxagliptine Sandoz.

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

Important identified risks	• Hypersensitivity reactions • Pancreatitis • Infections • Gastrointestinal-related AEs
Important potential risks	• Skin lesions (ulcer, erosion, necrosis) • Lymphopenia • Hypoglycaemia • Severe cutaneous adverse reactions • Opportunistic infection • Pancreatic cancer • Cardiac failure
Missing information	• Paediatric safety • Pregnancy and breast feeding • Severe hepatic impairment • Immunocompromised patients • Malignancy/neoplasm

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 Onglyza. 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 not been evaluated via a user consultation study. A bridging report has been submitted. 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

Saxagliptine Sandoz 2.5 mg and 5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Onglyza 2.5 mg and 5 mg film-coated tablets. Onglyza 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 Saxagliptine Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 May 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