COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ambrisentan Sandoz 5 mg and 10 mg, film-coated tablets (ambrisentan)

NL/H/6009/001-002/DC

Date: 16 July 2024

This module reflects the scientific discussion for the approval of Ambrisentan Sandoz 5 mg and 10 mg, film-coated tablets. The procedure was finalised at 10 September 2019 in Ireland (IE/H/0585/001-002/DC). After a transfer on 16 October 2023, the current RMS is the Netherlands. 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
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 data on quality, safety and efficacy, the Member States have granted a marketing authorisation for Ambrisentan Sandoz 5 mg and 10 mg, film-coated tablets from Sandoz B.V. on 10 September 2019 for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment.

A comprehensive description of the up-to-date indications and posology is given in the current SmPC.

This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a generic application. This means that the Ambrisentan Sandoz, film-coated tablets (5 mg and 10 mg) have the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Volibris film coated tablet 5mg and 10mg (the reference product) and that bioequivalence has been demonstrated with the reference product.

Ambrisentan Sandoz is a prescription only medicine.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Denmark, Germany, Spain and Sweden. Spain has withdrawn as a concerned member state on 11 January 2024.

II. QUALITY ASPECTS

II.1 Introduction

This application is for Ambrisentan Sandoz 5 mg and 10 mg, film-coated tablets.

II.2 Drug Substance

Manufacturing process

The active substance is ambrisentan an established active substance and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets current regulatory requirements.

Stability of drug substance
Batch analytical data demonstrating compliance with the active substance specification has been provided.

II.3 Medicinal Product

The medicinal product contains either 5 mg or 10 mg of the drug substance ambrisentan. The excipients in the medicinal product are listed in section 6.1 of the SmPC.

A visual description of the product is included in section 3 of the SmPC.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Manufacturing process
The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

Control of excipients
All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

Quality control of drug product
The Finished Product Specification is based on the pharmacopoeial monograph for the tablet dosage form, and the tests and control limits are considered appropriate for this type of product. The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

Packaging material
The approved packaging for this product is described in section 6.5 of the SmPC.
Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

Stability of drug product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Ambrisentan 5 mg and 10 mg Film-coated Tablets.

III. NON-CLINICAL ASPECTS

This active substance is a generic formulation of Volibris, which has been on the European market since 2008. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of ambrisentan are well known. As ambrisentan is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ambrisentan 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

The pharmacodynamic, pharmacokinetic and toxicological properties of ambrisentan are well known. As ambrisentan is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ambrisentan is a well-known active substance with established efficacy and tolerability. Ambrisentan is used in the treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Volibris marketed by GlaxoSmithKline.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Ambrisentan film coated tablet 10mg is compared with the pharmacokinetic profile of the reference product Volibris film coated tablet 10mg (GlaxoSmithKline).

The Member States have been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Ambrisentan is absorbed rapidly in humans. After oral administration, maximum plasma concentrations (Cmax) of ambrisentan typically occur around 1.5 hours post-dose under both fasted and fed conditions. Cmax and area under the plasma concentration-time curve (AUC) increase dose proportionally over the therapeutic dose range. Steady-state is generally achieved following 4 days of repeat dosing.
A food-effect study involving administration of ambrisentan to healthy volunteers under fasting conditions and with a high-fat meal indicated that the Cmax was decreased 12% while the AUC remained unchanged. This decrease in peak concentration is not clinically significant, and therefore ambrisentan can be taken with or without food.

Ambrisentan is highly plasma protein bound. The in vitro plasma protein binding of ambrisentan was, on average, 98.8% and independent of concentration over the range of 0.2 – 20 microgram/ml. Ambrisentan is primarily bound to albumin (96.5%) and to a lesser extent to alpha1-acid glycoprotein. The distribution of ambrisentan into red blood cells is low, with a mean blood-plasma ratio of 0.57 and 0.61 in males and females, respectively.

Ambrisentan is glucuronidated via several UGT isoenzymes (UGT1A9S, UGT2B7S and UGT1A3S) to form ambrisentan glucuronide (13%). Ambrisentan also undergoes oxidative metabolism mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19 to form 4-hydroxymethyl ambrisentan (21%) which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide (5%). The binding affinity of 4-hydroxymethyl ambrisentan for the human endothelin receptor is 65-fold less than ambrisentan. Therefore at concentrations

observed in the plasma (approximately 4% relative to parent ambrisentan), 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

Ambrisentan and its metabolites are eliminated primarily in the bile following hepatic and/or extra-hepatic metabolism. Approximately 22% of the administered dose is recovered in the urine following oral administration with 3.3% being unchanged ambrisentan. Plasma elimination half-life in humans ranges from 13.6 to 16.5 hours.

Bioequivalence studies

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Ambrisentan Sandoz 10 mg, film-coated tablet was compared to the reference product Volibris film coated tablet 10mg (GlaxoSmithKline).
Based on the pharmacokinetic parameters of active substance, the reference tablet Volibris film coated tablet 10mg marketed by GlaxoSmithKline and test tablet Ambrisentan Sandoz 10 mg film-coated tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The Ambrisentan Sandoz 5 mg, film-coated tablets are dose proportional with the Ambrisentan Sandoz 10 mg, film-coated tablet. The pharmacokinetics of the active substance are linear (dose proportional) over the therapeutic dose range (5 to 10mg). The results of the bioequivalence study performed with the Ambrisentan Sandoz 10 mg, film-coated tablet therefore apply to the other strengths.

IV.3 Pharmacodynamics

Ambrisentan is an orally active, propanoic acid-class, ERA selective for the endothelin A (ET A) receptor. Endothelin plays a significant role in the pathophysiology of PAH. Ambrisentan is a potent (Ki 0.016 nM) and highly selective ET A antagonist (approximately 4000-fold more selective for ETA as compared to ETB).

Ambrisentan blocks the ETA receptor subtype, localized predominantly on vascular smooth muscle cells and cardiac myocytes. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.
The selectivity of ambrisentan for the ETA over the ETB receptor is expected to retain ETB receptor mediated production of the vasodilators nitric oxide and prostacyclin.

IV.4 Clinical Efficacy

The efficacy of Ambrisentan Sandoz is well characterised.

IV.5 Clinical Safety

The safety of Ambrisentan Sandoz is well characterised.

IV.6 Risk Management Plan

Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.7 Discussion on the clinical aspects

For generic applications usually bioequivalence studies to demonstrate essential similarity to the product are carried out on a limited number of patients to avoid the need for repetitive tests on humans.
The applicant has submitted one bioequivalence study in the higher dose of 10mg carried out in the fasted state under standardised conditions in 36 adult males, with Volibris 10mg film coated tablet as the reference product. Dissolution studies were also submitted. The test/reference ratio and 90% confidence intervals for AUC0-t and Cmax fell well inside the acceptance criteria of 80 to 125% for determining bioequivalence.
A biowaiver was sought for the 5mg dose formulation. Conditions for the biowaiver were met. Therefore, the results of the bioequivalence study performed with the Ambrisentan Sandoz 10 mg, film-coated tablets therefore apply to the other strengths.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ambrisentan Sandoz is a medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The Member States, on the basis of the data submitted considered that Ambrisentan Sandoz 10 mg, film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

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
NL/H/6009/001-002/IA/010	**Type IA: B.I.b.1.b** *Tightening of specification limits. The total impurities specification is revised from 'Not more than 1.0%' to 'Not more than 0.50%'.*	No	26-01-2024	Yes	N.A.
NL/H/6009/001-002/R/001	Renewal	No	05-07-2024	Yes	N.A.