COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Ambrisentan Zentiva 5 mg and 10 mg film-coated tablets

# (ambrisentan)

# NL/H/4898/001-002/DC

# Date: 1 April 2021

**This module reflects the scientific discussion for the approval of Ambrisentan Zentiva 5 mg and 10 mg film-coated tablets. The procedure was finalised at 11 November 2020. 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 Ambrisentan Zentiva 5 mg and 10 mg film-coated tablets, from Zentiva k.s.

The product is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

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 Volibris 5 mg and 10 mg film-coated tablets which has been registered in the EEA by GlaxoSmithKline (Ireland) Ltd. since 21 April 2008 via a centralised procedure (EU/1/08/451).

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Germany, Estonia, France, Italia, Lithuania, Latvia, Poland, Romania, Slovak Republic and the United Kingdom.

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

Similarity assessment in view of the orphan drug legislation

The MAH provided a similarity assessment between Ambrisentan Zentiva (Ambrisentan), Opsumit (Macitentan), and Adempas (Riociguat) for the treatment of pulmonary arterial hypertension, taking into account the Commission Regulation (EC) No 847/2000 and the Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No. 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity (2008/C 242/08). It has been concluded that Ambrisentan Zentiva is not considered similar to Adempas or Opsumit, and therefore, the existence of any market exclusivity for any of these products will not prevent the granting of the marketing authorisation of Ambrisentan Zentiva.

# II. QUALITY ASPECTS

## II.1 Introduction

The 5 mg strength tablet is a pale-pink coloured, square shaped, biconvex, film-coated tablet, debossed with '5' on one side and plain on the other side. Each tablet contains 5 mg of ambrisentan.
The 10 mg strength tablet is a deep-pink coloured, oval shaped, biconvex film-coated tablet, debossed with '10' on one side and plain on the other side. Each tablet contains 10 mg of ambrisentan.

The film-coated tablets are packed in white PVC/PVDC/Aluminium blisters and transparent PVC/PE/PVDC blisters.

The excipients are:
*Tablet core* - lactose monohydrate, microcrystalline cellulose (E460), croscarmellose, sodium (E468) and magnesium stearate (E572)
*Film-coating* - polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171), macrogol/polyethylene glycol (E1521), lecithin (soya) (E322) and allura red AC (E129)

The core of the two tablet strengths are fully dose proportional.

## II.2 Drug Substance

The active substance is ambrisentan, an established active substance, however not described in the any pharmacopoeia (Ph.Eur.). Ambrisentan is a white to off-white crystalline powder and is soluble in methanol and ethanol and practically insoluble in water. It is a BSC Class II drug (low solubility and high permeability). The drug substance is present as the S-isomer. The R-isomer is controlled as an impurity. The drug substance exhibits polymorphism. The manufacturing process of the active substance manufacturer yields Form-M. Control of the polymorphic form is part of the drug substance specification.

The Active Substance Master File (ASMF) procedure is used for the active substance from two suppliers. 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 active substance is produced by three manufacturers. The synthesis route for the first manufacturer consists of three chemical steps and for the second manufacturer of five linear synthetic steps followed by a single purification stage. The third manufacturer uses a synthesis route that consists of five chemical steps and a final purification. The drug substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The drug substance specification is established in-house and contains tests for appearance, identification, water content, sulphated ash, specific optical rotation, related substances, impurities, Assay, R-isomer, residual solvents, benzene and particle size. It is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two batches from both suppliers demonstrating compliance with the drug substance specification.

Stability of drug substance

*Manufacturer one* – stability data on the active substance have been provided for three commercial scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). All results remain within specification up to 48 months. Based on the stability data provided, the claimed re-test period of 36 months with storage condition "Store in a well closed container below 30°C, excursions permitted up to 40°C", are regarded justified.

*Manufacturer two* - stability data on the active substance have been provided for three commercial scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). The stability testing results are well within the acceptance criteria. Based on the presented stability data, a re-test period of 36 months can be granted when stored under the proposed conditions.

*Manufacturer three* - Stability data on the active substance have been provided for three production batches stored at 25°C/60% RH (72 months) and 40°C/75% RH (6 months). Based on the stability data provided a re-test period of 60 months is considered acceptable if stored in in a well closed container between 20°C and 25°C (excursions allowed between 15°C and 30°C)

## 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 were formulation development, dissolution method development and manufacturing process development.

Development of the proposed routine dissolution method has been adequately described. The proposed acceptance criterion takes the dissolution profile of the biobatch sufficiently into account. The discriminatory nature of the method was shown with a drug product batch containing a coarser drug substance.

A bioequivalence study was carried out with the 10 mg strength of the test product and of the reference product Volibris. The comparative dissolution data of the bio batches in 0.1 N HCl, pH 4.5 acetate buffer, pH 5.0 acetate buffer (QC medium), and pH 6.8 phosphate buffer support bioequivalence. A biowaiver was requested for the 5 mg strength.

Manufacturing process

The manufacturing process consists of geometrical blending, final mixing, compression, coating, quality control and packaging and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients

Apart from the coating mix, all excipients comply with the Ph.Eur. The components of the coating mix comply with the Ph. Eur. or (EU) No 231/2012 legislation. The 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, length/width, water content, disintegration time, dissolution, uniformity of dosage units (content uniformity), assay, related substances, identification of coloring agent 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 have been provided for six batches of each strength stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in opaque PVC/PVdC–Al blisters. No significant trend or changes have been observed. The claimed shelf life of 36 months without any special storage conditions on temperature is justified.

Results of photostability studies have been provided that demonstrate that not only the unpacked tablets but also the tablets in the transparent PVC/PE/PVDC blister packaging are sensitive for light. Although assay and levels of impurities are not impacted, the colour of tablets bleaches. In view of that a specific storage condition for the tablets in the PVC/PE/PVDC – Aluminium blister packaging must be applied ‘Keep the blister in the outer carton to protect from light’.

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

Lactose is sourced from healthy cows in the same conditions as milk collected for human consumption. TSE/BSE 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 Ambrisentan Zentiva 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 Ambrisentan Zentiva 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 Volibris 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

Ambrisentan 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 Ambrisentan Zentiva 5 mg and 10 mg film-coated tablets (Centrafarm B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Volibris 5 mg and 10 mg film-coated tablets (GlaxoSmithKline (Ireland) Ltd., Ireland).

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

Biowaiver

A biowaiver is requested for the 5 mg strength. The following conditions are fulfilled:

- Ambrisentan displays linear pharmacokinetics.
- The 10 mg and 5 mg strengths of the test preparation have the same qualitative composition.
- The 10 mg and 5 mg strengths of the test preparation are dose proportional.
- Both tablets have the same manufacturing process.
- Appropriate in vitro dissolution data are available at three pH

The justification for the biowaiver of strength for the 5 mg, film-coated tablet is acceptable and therefore the biowaiver 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 30 healthy male subjects, aged 18-50 years. Each subject received a single dose (10 mg) of one of the 2 ambrisentan formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected at 0.0 (pre-dose) and at 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 60.00 and 72.00 hours after administration of the products.

The design of the study is acceptable.

Ambrisentan may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of Ambrisentan. 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.

*Results*
Three subjects withdrew from the study due to personal reasons. Therefore, a total of 27 subjects completed the study and were eligible for pharmacokinetic analysis.

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

| Treatment N=27 | $AUC_{0-t}$ (ng.h/ml) | $AUC_{0-\infty}$ (ng.h/ml) | $C_{max}$ (ng/ml) | $t_{max}$ (h) | $t_{½el}$ (h) |
|---|---|---|---|---|---|
| **Test** | 7119 ± 2303 | 7570 ± 2386 | 939 ± 185 | 1.33 (0.5-2.5) | 18 ± 5 |
| **Reference** | 7053 ± 2158 | 7522 ± 2224 | 889 ± 170 | 1.33 (0.5-3) | 19 ± 6 |
| ***Ratio (90% CI)** | 1.00 (0.96 – 1.05) | -- | 1.06 (0.98 – 1.14) | -- | |
| **CV (%)** | 8.6 | -- | 16.3 | -- | |

**$AUC_{0-\infty}$** 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 Ambrisentan Zentiva is considered bioequivalent with Volibris.

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 Ambrisentan Zentiva.

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

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|---|---|
| Important identified risks | • Teratogenicity<br>• Decreased haemoglobin, haematocrit, anaemia, including anaemia requiring transfusion<br>• Hepatotoxicity |
| Important potential risks | • Testicular tubular atrophy/male infertility |
| Missing information | None |

The MAH shall ensure that in each Member State where ambrisentan is marketed, all patients who are expected to use ambrisentan are provided with the following educational material:

- Patient reminder card

Patient reminder card should include the following key elements:

- That treatment may increase the risk of teratogenicity and liver injury as described in the patient leaflet;
- That ambrisentan is teratogenic in animals;
- That pregnant women must not take ambrisentan;
- That women of reproductive potential must use effective contraception;
- The need for monthly pregnancy tests;
- The need for regular monitoring of liver function because ambrisentan may cause liver injury.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Volibris. 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 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

Ambrisentan Zentiva 5 mg and 10 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Volibris 5 mg and 10 mg film-coated tablets. Volibris 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 Ambrisentan Zentiva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 November 2020.

## 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 |
|---|---|---|---|---|---|
| | | | | | |