COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ambrisentan Devatis 5 mg and 10 mg film-coated tablets

(ambrisentan)

NL/H/4437/001-002/DC

Date: 27 January 2020

This module reflects the scientific discussion for the approval of Ambrisentan Devatis 5 mg and 10 mg film-coated tablets. The procedure was finalised at 22 Augustus 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
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 Devatis 5 mg and 10 mg film-coated tablets, from Devatis GmbH.

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 state (CMS) involved in this procedure was Germany.

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

Scientific advice

The MAH has received scientific advice on 26 November 2014 from the German medicine authority BfArM regarding the proposed batch size and the approach in regards to the bioequivalence study.

Similarity assessment in view of the orphan drug legislation

The MAH provided a similarity assessment between Ambrisentan Devatis (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 Devatis 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 Devatis.

II. QUALITY ASPECTS

II.1 Introduction

The 5 mg strength tablet is a pale-pink coloured, square shaped, biconvex, film-coated tablet and contains 5 mg of ambrisentan.
The 10 mg strength tablet is a deep-pink coloured, oval shaped, biconvex film-coated tablet and contains 10 mg of ambrisentan.

The film-coated tablets are packed in PVC/PVDC/aluminium foil blisters with heat seal lacquer.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460(i)), croscarmellose, sodium (E468) and magnesium stearate (E470b)
Film-coating - polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171), macrogol (E1521), lecithin (soya) (E322) and allura red AC aluminium lake (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 any pharmacopoeia. Ambrisentan is a white to off-white crystalline powder and is soluble in methanol and ethanol and practically insoluble in purified 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. 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 consists of six steps. The last step is a purification step. No Class I organic solvents or metal catalysts are used. The drug substance is micronized by the active substance manufacturer. 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 of the drug product manufacturer is identical to that of the ASMF holder except for an additional requirement for particle size distribution. It is considered adequate to control the quality. The specification contains tests for appearance, solubility, identification, water, heavy metals, sulphated ash, particle size, assay, enantiomeric purity, residual solvents, polymorph and related substances. Batch analytical data demonstrating compliance with this specification have been provided for one commercial scale and two pilot scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three commercial scale batches and one smaller micronized batch stored at 25°C/60% RH (60 months) and 40°C/75% RH (six months, commercial scale batches only). No trends or deviations were observed. Based on the data submitted, a retest period could be granted of 60 months without specific storage 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 ant their functions explained. Formulation development was based on using the same excipients as the reference products and a direct compression approach. Formulation development studies focused on grades and amounts of the components. Sufficient information has been provided on manufacturing process development. The choices of the packaging and manufacturing process are justified.

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 biobatches 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 dry mixing, compression and film-coating and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scale batches in accordance with the relevant European guidelines.

Control of excipients

Apart from Allura Red, all excipients comply with the Ph.Eur. Acceptable in-house specifications were defined for the coating materials. The choice of functionality-related characteristics described in the Ph.Eur. monographs for lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate have been adequately justified. 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, average weight, thickness, length, width, identification, assay, dissolution, uniformity of dosage units, water, hardness, disintegration, related substances, enantiomeric purity and microbiological controls. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf life specifications are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full-scale 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 three full-scale batches of each strength stored at 25°C/60% RH (36 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 drug product was shown to be photo stable outside the primary packaging. The claimed shelf life of 36 months without any special storage conditions is justified.

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

Compliance with Note for *Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products* has been confirmed for lactose monohydrate.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ambrisentan Devatis 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 Devatis 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 Devatis 5 mg and 10 mg film-coated tablets (Devatis GmbH, Germany) 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.
- Comparative dissolution data at pH 1.2, 4.5 and 6.8, using a speed of 50 rpm, showed that dissolution was comparable for the 5 and 10 mg tablet.

The justification for the biowaiver for the 5 mg strength 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 20 healthy male subjects, aged 18-45 years. Each subject received a single dose (10 mg) of one of the 2 ambrisentan formulations. The tablet was orally administered with water after an overnight fast of at least eight hours. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected at 0.0 (pre-dose) and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 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

One subject was discontinued due to protocol violation, as his urine test was found to be positive for THC. Therefore, 19 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	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	t_{max}

N=19	(ng.h/ml)	(ng.h/ml)	(ng/ml)	(h)
Test	7858 ± 1621	8071 ± 1641	1168 ± 208	1.8 (0.7-5.0)
Reference	7970 ± 1446	8210 ± 1476	1212 ± 199	2.3 (0.7-4.5)
***Ratio (90% CI)**	0.98 (0.95 – 1.01)	0.98 (0.95 – 1.01)	0.96 (0.89 – 1.04)	--
CV (%)	5.3	5.1	14.0	--

$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ambrisentan Devatis 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 Devatis.

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

Important identified risks	• Teratogenicity • Decreased haemoglobin, haematocrit, anaemia, including anaemia requiring transfusion • 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 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

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 the originator product Volibris 5 mg and 10 mg film-coated tablets for the content and to Hydroxycarbamid Devatis 500 mg Hartkapseln (DE/H/5243/001-DC) for the lay-out. 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

Ambrisentan Devatis 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 Devatis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 August 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