EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2019
EMA/CHMP/294468/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ambrisentan Mylan

International non-proprietary name: ambrisentan

Procedure No. EMEA/H/C/004985/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Ambrisentan Mylan
Applicant:	MYLAN S.A.S 117 Allee des Parcs 69800 Saint-Priest FRANCE
Active substance:	AMBRISENTAN
International non-proprietary name/Common name:	ambrisentan
Pharmaco-therapeutic group (ATC Code):	other antihypertensives, antihypertensives for pulmonary arterial hypertension (C02KX02)
Therapeutic indication(s):	Ambrisentan Mylan 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.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	5 mg and 10 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PVdC/alu)
Package size(s):	30 tablets and 30 x 1 tablets (unit dose)

Table of contents

List of abbreviations

ANOVA	Analysis of Variance
AE	Adverse event
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
% CV	% Coefficient of Variation
CI	Confidence Intervals
CMAX	Maximum Plasma Concentration
CQA	Critical Quality Attribute
CV	Coefficient of Variation
EC	European Commission
EU	European Union
FC	Functional class
GLM	General linear model
GLP	Good laboratory practice
GC	Gas Chromatograph
GCP	Good clinical practice
HIV	Human immunodeficiency virus
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Institutional ethical committee
IR	Infrared
KEL	Elimination Rate Constant
KF	Karl Fischer titration
LDPE	Low density polyethylene
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PAH	Pulmonary arterial hypertension
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QSAR	Quantitative structure activity relationship
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative Humidity
SD	Standard Deviation
S E	Standard Error
SmPC	Summary of Product Characteristics
SAS	Statistical Analysis Software
TMAX	Plasma Concentration Reaches a Peak
T1/2	The Elimination Half-Life
TLC	Thin layer chromatography
TMAX	Time of The Maximum Measured Plasma Concentration
TSE	Transmissible Spongiform Encephalopathy
VD	Volume of Distribution
UV	Ultraviolet
WHO	World health organization
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S submitted on 30 April 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Ambrisentan Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2018.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: Ambrisentan Mylan 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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Volibris instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Volibris 5/10 mg film-coated tablets
- Marketing authorisation holder: Glaxo Group Ltd
- Date of authorisation: (21-04-2008)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/451

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Volibris 5/10 mg film-coated tablets
- Marketing authorisation holder: Glaxo Group Ltd
- Date of authorisation: (21-04-2008)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/451

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Volibris 5/10 mg film-coated tablets
- Marketing authorisation holder: Glaxo Group Ltd
- Date of authorisation: (21-04-2008)
- Marketing authorisation granted by:

- Union
- Marketing authorisation numbers: EU/1/08/451/001-004

- Bioavailability study number: C17139

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Eleftheria Nikolaidi

The application was received by the EMA on	30 April 2018
The procedure started on	24 May 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 August 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 August 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 September 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	4 January 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	4 February 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 February 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	28 February 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	09 April 2019

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ambrisentan Mylan on	26 April 2019
The CHMP adopted a report on similarity of Adempas and Opsumit	26 April 2019

2. Scientific discussion

2.1. Introduction

Ambrisentan Mylan is a proposed generic product of Volibris which is indicated for pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment.

The proposed product is an immediate release film-coated 5mg and 10 mg tablets containing ambrisentan as an active substance and the recommended dose is 5 mg once daily which may be increased to 10 mg daily depending upon clinical response and tolerability.

Ambrisentan was first introduced into the market in Europe not less than eight years ago as Volibris film coated tablets. This Marketing Authorisation Application (MAA) is made on the basis that Ambrisentan film-coated tablets 5/10 mg is essentially similar to Volibris 5/10 mg film-coated tablets in accordance with Article 10(1) (a) (iii) of Directive 2001/83/EC. The indications sought are the same as those for Volibris 5/10 mg film-coated tablets.

As this is an abridged license application claiming essential similarity to a currently marketed product, no clinical studies have been undertaken to support the application. One bioequivalence study was undertaken comparing Ambrisentan Mylan film coated tablets 10 mg against Volibris 10 mg film coated tablets under fasting conditions.

In addition, the Applicant made reference to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – January. 2010) and provided justification in order to prove that Ambrisentan 5 mg film-coated tablets satisfy the conditions for waiver of bioequivalence studies conducted with Ambrisentan 10 mg film-coated tablets.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 5 and 10 mg of Ambrisentan as active substance.

Other ingredients are:

Tablet core: lactose, microcrystalline cellulose (E460i), croscarmellose sodium and magnesium stearate.

Film coat: poly(vinyl alcohol) partly hydrolysed, titanium dioxide (E171), macrogol, talc (E553b), allura red AC aluminium lake (E129) and indigo carmine aluminium lake (E132).

The product is available in PVC/PVDC blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of ambrisentan is (+)-(*2S*)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid corresponding to the molecular formula $C_{22}H_{22}N_2O_4$. It has a relative molecular mass of 378.42 g/mol and the following structure:

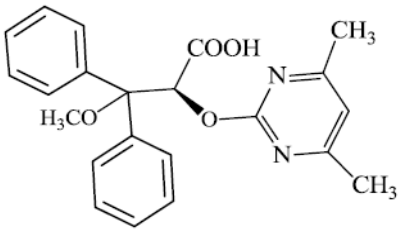


Figure 1: active substance structure

The chemical structure of ambrisentan was elucidated by a combination of IR, UV, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis. The solid state properties of the active substance were measured by XRPD, melting point and laser diffraction.

Ambrisentan is a white to off-white powder, non-hygroscopic, slightly soluble in methanol and practically insoluble in water. It is slightly soluble in alkaline buffers (pH 6.8 and 8.0). The active substance is considered to be a “low solubility and high permeability drug” (BCS Class 2).

Ambrisentan exhibits stereoisomerism due to the presence of one chiral centre. The material manufactured is consistently *S* (+) isomer. Enantiomeric purity is controlled routinely by chiral HPLC and specific optical rotation.

Polymorphism has been observed for the active substance. Different forms Form-M, Form-R, Form-V, Form-VI, crystalline form, Form-I, DMSO co-crystal form and stabilized amorphous form are reported in the literature. Consistent manufacture of the same polymorphic form is confirmed by the manufacturer, at release, during storage and under stress (high temperature, humidity and photolytic) conditions.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is synthesized using commercially available well defined starting materials with acceptable specifications. The manufacturing process has been validated. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were discussed with regards to their origin and characterised. Specifications for the reagents, solvents and processing aids are included. The limits proposed are found sufficient to comply with the ICH Q3C (R6) requirements. Details on the origin of process related impurities and degradation products including formation pathways have been provided and it has been demonstrated that all potential impurities (including the chiral and genotoxic impurities) are controlled in isolated intermediates or the final active substance. All compounds involved in the synthesis of the active substance, including starting materials, intermediates, solvents and reagents have been assessed for

QSAR Alerts. Application of the guideline ICH M7 and an adequate control strategy for each compound have been presented. Discussion and risk assessment on elemental impurities as per ICH Q3D guideline has been submitted.

The active substance is packed in a LDPE bag, which complies with the EC directive 2002/72/EC and EC 10/2011 as amended, inserted in a black polythene bag and further placed in HDPE drums.

Specification

The active substance specification includes tests for: appearance, solubility, identity (IR, HPLC, XRPD, specific optical rotation), water content (KF), sulphated ash (Ph. Eur.) assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), impurities (UPLC), residual solvents (GC) and particle size (laser diffraction).

Although the active substance is non-sterile and the finished product is an oral dosage form, three consecutive production scale batches of ambrisentan were tested for total aerobic microbial count, total combined molds and yeast count and specified microorganisms. Microbial growth was not observed for specified microbial species justifying the omission of a test for microbial limits in the active substance specification.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of 3 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification (IR, HPLC), water content, related substances, enantiomeric purity, and assay. Samples stored under accelerated conditions were also tested for polymorphic form (XRPD) and impurities by UPLC. The analytical methods used were the same as for release. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions were also provided. It is concluded that the active substance is not sensitive to base, oxidation, thermal and UV radiation conditions. In the acidic conditions, the only degradation peak corresponds to decarboxylate impurity. These results demonstrate the stability indicating nature of the HPLC method used for the determination of assay and related substances.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The immediate release, film-coated tablets are packaged in PVC/PVDC blister packs comprised of clear to almost clear, transparent PVC coated with PVDC on one side and hard tempered aluminium foil coated with heat seal lacquer on other side.

The 5 mg tablet is a pink, film-coated, round, biconvex tablet debossed with 'M' on one side of the tablet and 'AN' on the other side. Diameter: approximately 5.7 mm.

The 10 mg tablet is a pink, film-coated, capsule shaped, biconvex tablet debossed with 'M' on one side of the tablet and 'AN1' on the other side. Dimensions: approximately 9.9 mm × 4.8 mm.

The purpose of the pharmaceutical development studies was to develop an essentially similar, generic version of the branded formulation (Volibris). The product should be suitable for large-scale manufacture and demonstrate acceptable stability performance in the proposed marketing pack.

The quality target product profile (QTPP) was based on the properties of the active substance, characterisation of the reference product, consideration of the reference product label and intended patient population. The QTPP was defined as 5 mg and 10 mg oral immediate release tablets, bioequivalent to the reference product, with a shelf-life of at least 24 months at room temperature in a blister or HDPE bottle with defined quality attributes (identification, assay, content uniformity, related substances, dissolution, water content and microbial tests).

Identification of critical quality attributes (CQAs) was based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attributes of the finished product. Risk assessment was performed to identify the formulation variables affecting the proposed CQAs. The identified formulation variables were studied at various levels and the optimized level of each variable was selected based on the desired values of the CQAs. An updated formulation risk assessment was found to be satisfactory as the high and medium formulation risks were reduced to low.

Following formulation risk assessment, a similar risk assessment was conducted to evaluate the risk associated with various manufacturing process variables like blending, lubrication and compression. Formulations were prepared employing different levels of each process variable and evaluated for the affected CQAs. The final ranges for each process parameters were determined based on the results of these studies. Subsequently, the risk assessment was updated after process development to capture the reduced level of risk based on improved process understanding.

Various physico-chemical characteristics of the active substance were considered during the development of the product: particle size distribution, apparent density, tapped density, compressibility index, Hausner ratio, flowability (very poor), solubility (increasing as pH increases), melting point, pKa (4.0), polymorphism isomerism is controlled in the active substance specification), hygroscopicity (non-hygroscopic) and compatibility with the excipients selected (in terms of the insignificant increase of the total impurities after 4 weeks accelerated storage of different binary mixtures of the active substance and each excipient).

The excipients used in ambrisentan tablets were selected based on the excipients used in the reference product, drug-excipient compatibility study and their functionality. The drug-excipient compatibility study showed that active substance is compatible with all the excipients used for the study. Except film coating material, all the excipients used are conventional pharmaceutical ingredients that comply with the requirements of the European Pharmacopoeia. The film coating materials is proprietary material purchased from an established commercial supplier, to an agreed specification. The individual compendial components used in the manufacturing of Opadry coating material comply with the monograph in Ph. Eur. The colorants used in Opadry coating material comply with directive (EU) No.231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Various formulation optimization studies were also conducted (regarding diluents, disintegrant, lubricant, active substance particle size and filmcoating weight). The formula selected was the one that showed comparable disintegration time and dissolution profile to that of reference product.

Comparative dissolution profiles of the Applicant's ambrisentan 5 mg and 10 mg film-coated tablets and the reference product Volibris 5 and 10 mg film-coated tablets were generated in different dissolution media

The comparison of the test product strength used in the bioequivalence study (10 mg) and the other strength (5mg) showed that the *in vitro* release profile of test product is similar to that of reference product and also as demonstrated in the *in vivo* bio-equivalence study. Based on the results and similarity factor (f2 values), it is concluded that dissolution profiles of test product used in bioequivalence study (10 mg) and other strength of test product (5 mg) was found to be similar in all the media covering the pH range of 1.2 to 6.8 at 50 rpm as per the requirement of the Guideline on the Investigation of Bioequivalence and hence request the Agency to grant biowaiver for Ambrisentan 5mg film-coated tablets.

The release profile of lower strength across the physiological pH (1.2, 4.5 to 6.8) at 50 rpm as per the requirements of Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) is found to be similar as that of release profile of bio-test strength and reference product. Hence the requirement of bio-waiver for the lower strength is fulfilled.

The formulation used during clinical studies is the same as that intended for marketing.

In order to assess the ability of the selected dissolution method to discriminate between good (bio-equivalent) and bad formulations, the applicant has performed dissolution studies on different 10 mg batches formulated with slightly modified composition, and manufactured using different conditions. The batches formulated with variation in composition or manufactured using different processing conditions showed comparable dissolution with the intended batch formula. The discriminatory power of the dissolution method has been demonstrated.

Biowaiver justification for Ambrisentan 5 mg film-coated tablets was provided based on the fact:

-both the strengths of Ambrisentan film-coated tablets (5 mg and 10 mg) are manufactured by the same manufacturer at the same manufacturing site using the same manufacturing process;

-the excipients included on the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected;

-the qualitative composition of both strengths is the same. Both the strengths are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of the active substance is the same for both the strengths;

-both strengths exhibit similar in-vitro performance. The dissolution profiles are similar; and

-the absorption kinetics of ambrisentan is linear within the therapeutic dose range.

The bio-equivalence study results of Ambrisentan 10 mg film-coated tablets can be extended to Ambrisentan 5 mg film-coated tablets.

The manufacturing process was optimized for blending time for both pre-lubrication stage and lubrication stage with regard to blend uniformity, and tablet hardness (resistance to crushing) range, with regard to dissolution profile and in comparison with reference product.

To achieve this, trials were taken with different blending times and optimized based on blend uniformity. To evaluate the effect of tablet hardness on product characteristics, tablets were compressed at different hardness range and evaluated for physical parameters and dissolution.

There are no overages in the finished product.

Discussion and risk assessment on elemental impurities as per ICH Q3D guideline has been submitted.

The primary packaging is PVC/PVDC blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The in-process controls are adequate for this manufacturing process. A process validation protocol and relevant data are provided in the documentation. Additional commitment on the future validation of production scale batches and relevant process validation protocols at the higher edge of the proposed batch size are also provided.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, UV), dissolution (HPLC), uniformity of dosage (content uniformity), related substances (HPLC), assay (HPLC), water (KF), microbiological control (Ph. Eur.) and color identification (TLC).

Exactly the same specifications apply also for the 5 mg strength, except for appearance (a pink, film-coated, round, biconvex tablet debossed with `M' on one side of the tablet and `AN' on the other side)

No skip testing (other than colour identification and microbiological testing) is proposed.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 pilot scale batches (half of production scale) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 pilot scale batches (half of production scale) of each strength of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same tests as in Shelf life specifications. Stability indicating parameters studied include description, assay, dissolution, water content, related substances and microbiological test. The results found are well within the set specification limits and material balance (regarding assay and impurities results) is maintained at all times under all tested conditions.

One batch of ambrisentan tablets of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The study results indicated they were no out of specification results for assay, related substances and dissolution of tablets in the tablets exposed or protected from light, when compared to initial results. Thus, it can be concluded that ambrisentan tablets are photostable.

Bulk packs are proposed for holding the finished product before packaging or for transportation to any other approved re-packaging site in Europe. The data submitted supports a 12 months of holding time for the bulk package

Based on available stability data, the proposed shelf-life of 36 months and “This medicinal product does not require any special storage condition” as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

The applicant considered that consumption and population data over the last 4 years across 25 different Member States provide adequate justification for the absence of specific ERA study for Ambrisentan Mylan 5 and 10 mg. At the request of the CHMP, and using a prevalence for PAH of 26.0 per million, as the worst case scenario, based on available published data, the obtained $PEC_{SURFACEWATER}$ the action limit of 0.01 µg/L.

The partition coefficient (LogP) of Ambrisentan in Octanol/Water at 25°C was experimentally determined to be 1.21 ± 0.20, indicating a low potential for bioaccumulation.

2.3.3. Discussion on non-clinical aspects

As ambrisentan is a well-known active substance, no further studies concerning pharmacodynamic, pharmacokinetic and toxicological properties of this active substance are required. Therefore the submitted overview based on literature review was considered appropriate by the CHMP.

A valid justification for not submitting a full ERA was given. The estimated $PEC_{SURFACEWATER}$ for ambrisentan in Ambrisentan Mylan tablets was below the action limit of 0.01 µg/L as defined in the 'EMA Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA/CHMP/SWP/44609/2010)'. Furthermore, the partition coefficient (LogP) of Ambrisentan in Octanol/Water indicated a low potential for bioaccumulation and therefore it was agreed that no further evaluation of the environmental toxicity was needed.

2.3.4. Conclusion on the non-clinical aspects

The CHMP agreed that there are no objections to the approval of Ambrisentan Mylan from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for tablets containing ambrisentan. To support the marketing authorisation application the applicant conducted one bioequivalence study with a cross-over design under fasting conditions. This study was the pivotal study for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the EMA Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant requested a waiver of the bio-study for the lower (5 mg) strength. This requested was considered possible, as both strengths of the Ambrisentan Mylan film-coated tablets (5 mg and 10 mg) are manufactured by the same manufacturer at the same manufacturing site using the same manufacturing process, have the same qualitative composition. Furthermore, both strengths are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of the active substance is the same for both the strengths.

In order to demonstrate that both strengths exhibit similar *in vitro* performance, dissolution profiles of Ambrisentan 5 mg and 10 mg film-coated tablets (manufactured by Mylan Laboratories Limited, Nashik, India), were generated in different dissolution media i.e. 0.05M acetate buffer, pH 5.0 (Release media), 0.1N HCl, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer, covering the pH range of pH 1.2 to pH 6.8.

The similarity factor (F2 value) between the test product used in bioequivalence study, Ambrisentan Mylan 10mg, and the other strength of the test product, Ambrisentan Mylan 5mg in 0.1N HCl was found to be greater than 50 (81.49). More than 85% of the labeled amount of the drug is released within 15 minutes from both strengths tested in pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer. Thus acccording to the applicant the dissolution profiles could be considered similar.

However, the CHMP noted that the rotation speed used was 75rpm instead of the recommneded 50rpm in the BE Guideline. As this could have resulted in a rapid drug release, and thus a reduced discriminating power of the dissolution test, the applicant was requested to carry out appropriate dissolution tests of both strengths and submit the relevant dissolution data in all dissolution media (pH 1.2, 4.5 and 6.8) using the apparatus II-paddle at the rotation speed of 50rpm. These were provided by the applicant, and the F2 values between both strengths tested in 0.1N HCl and pH 4.5 Acetate buffer were found to be greater than 50 (53.79 and 56.64 respectively). More than 85% of the labeled amount of the drug is released within 15 minutes from both products tested in 0.05M acetate buffer pH 5.0 and pH 6.8 Phosphate buffer. Thus the dissolution profiles can be considered similar without further mathematical calculations

The applicant also noted that the absorption kinetics of ambrisentan is linear within the therapeutic dose range, as stated in the SmPC of the referecne product, and therefore one bioequivalence study performed on 10 mg strength would allow the *in vivo* performance to be extended to 5 mg strength.

Clinical studies

To support the application, the applicant has submitted a bioequivalence study.

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	Not Applicable								
BE	Project No. C17139	Clinical Study Report & PK Report and Adverse Event Listing **Clinical Study (5.3.1.2)** Bioanalytical Report **Bioanalytical (5.3.1.4)** CRFs and Individual Subjects **Individual CRF (5.3.7)** Literature References **Literature References (5.4)**	Primary objective: To evaluate the oral bioequivalence study of Ambrisentan Tablets 10 mg of Mylan Laboratories Limited, India with Volibris® (Ambrisentan) film-coated tablets 10 mg of Glaxo Group Ltd 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom in normal healthy adult male human subjects under fasting conditions Secondary objective: To monitor the adverse events and to ensure the safety of the study subjects.	An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study.	Test Drug (T): Ambrisentan Tablets 10 mg, 1x 10 mg, oral Reference Drug (R): Volibris® 10 mg (Ambrisentan), 1x 10 mg, oral	Planned - 36+ A maximum of 02 additional subjects Enrolled - 36 + 02 additional subjects (standby-I & standby-II) Dosed: Period-1: 36 Subjects Period-2: 35 Subjects Completed - 35 subjects Withdrawn: 01 subject (subject number 02) Bio-sample analyzed – 35 Subjects Pharmacokinetic and statistical data analyzed – 35 subjects.	Healthy, adult, human male subjects	Single-dose	Complete; Abbreviated

2.4.2. Pharmacokinetics

Study C17139: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Ambrisentan Tablets 10 mg of Mylan Laboratories Limited, India with Volibris (Ambrisentan) film-coated tablets 10 mg of Glaxo Group Ltd 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom in normal healthy adult male human subjects under fasting conditions.

Methods

Study design

The study was an open-label, randomized, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study in normal healthy adult male human subjects under fasting conditions.

Allocation of treatment sequence for each subject in each study period was carried out as per the randomization schedule.

In each period, all subjects had fasted overnight for at least 10.00 hours prior to dosing till at least 04.00 hours after dosing. In each study period, a single oral dose of either test product (T) or reference product (R) were administered orally to the subjects in sitting posture with 240 mL of water at ambient temperature on the day of dosing as per the randomization schedule.

Serial blood sampling from pre-dose 0.00 hour (within 1.50 hour prior to drug administration) up to post-dose 72.00 hours (after drug administration) was collected in each period.

The total duration of the study was 12 days from period-1 check-in till the last blood sample collection of period-2 including a washout period of 07 days between each dosing.

Test and reference products

Table 2. Test and reference product information in Study C17139

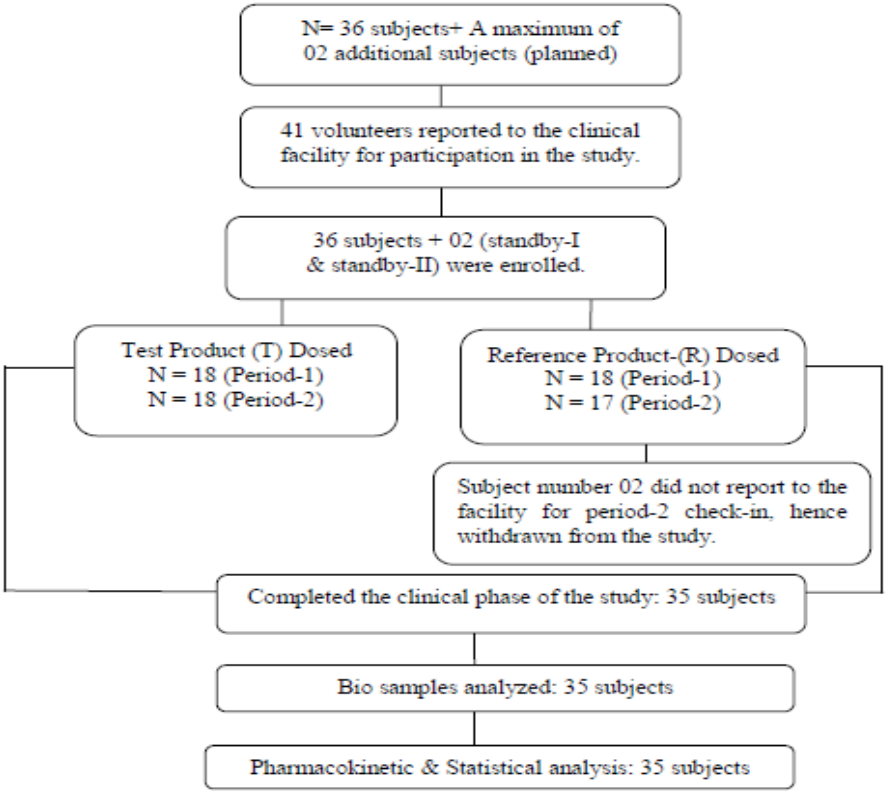
Product Characteristics	Test Product	Reference Product
Name	Ambrisentan Tablets	Volibris® Ambrisentan
Strength	10 mg	10 mg
Dosage Form	Tablets	Tablets
Manufactured by	**Manufactured by:** Mylan Laboratories Limited, F-4 & F-12, MIDC, Malegaon, Sinnar, Nasik, 422113, Maharashtra, India.	**Distributed by:** Glaxo Group Ltd 980 Great West Road Brentford Middlesex TW8 9GS, Storbritannien/ ISO-Britannia.
Batch number/ Lot number	2007505	WSFM
Batch Size (Biobatch)	1,30,000	Not available
Measured Content(s) (% of Label Claim)	100.7 % w/w	100.9 % w/w
Commercial Batch Size	Not applicable	Not available
Expiry Date	Aug 2017	04/2018
Location of Certificate of Analysis	5312-compar-ba-be-stud-rep, Appendix-16.1.7	5312-compar-ba-be-stud-rep, Appendix-16.1.7
Member State where the reference product is purchased from:	Not applicable	United Kingdom
This product was used in the following trials:	Study no.: C17139	Study no.: C17139

Population studied

From the eligible volunteers reported to the facility for participation in the study, 36 subjects were enrolled into the study. Two additional subjects (standby-I & standby-II) were enrolled in the study to compensate any dropout/withdrawn prior to dosing in period-1.

The disposition of the subjects in the study is depicted in **Figure 4**.

Figure 2. Disposition of subjects in Study C17139



Subjects were included based on the following criteria:

- Normal healthy male adult human subjects, aged between 18 to 45 years (inclusive of both)
- Body mass index of ≥18.5 kg/m2 and ≤ 30.0 kg/m2 and weight ≥ 50.00 kg with hemoglobin levels ≥ 12 g/dL.
- Healthy according to the laboratory results and physical examination, performed within 21 days prior to the commencement of the dosing in Period-1.
- Subject whose clinical laboratory values are within normal limits or clinically insignificant as determined by physician or principal investigator to be of no clinical significance.
- Had normal ECG, Chest X-ray and vital signs
- Non-smokers and Non-alcoholics
- Subject able to communicate effectively and provide written informed consent.
- Willing to avoid sexual contact during the study including the washout period.
- Subject willing to adhere to protocol requirements as evidenced by written informed consent approved by an Independent Ethics Committee (IEC).

Subjects were excluded based on the following criteria:

- Any history of allergy or hypersensitivity to Ambrisentan, to soya, or to any of the excipients and/or related products.
- Positive test result for hepatitis B surface antigen (HBs Ag), hepatitis C virus antibody (HCV Ab) or HIV-1 antibody or HIV Type 2 (HIV-2) antibody (HIV Ab) or VDRL / syphilis.
- The study drug is contraindicated for medical reasons (as stated in protocol).
- Any history or presence of significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, dermatological, neurological, psychiatric diseases or disorders.
- History or presence of drug abuse in the past one year.
- Difficulty in swallowing tablets or capsules.
- Any history of difficulty in donating blood.
- Has clinically significant abnormal values of laboratory parameters.
- Blood pressure is < 100/60 and > 140/90 millimeters of mercury (Systolic blood pressure/ Diastolic blood pressure).
- Pulse rate less than 60 beats / minute and more than 100 beats / minute.
- Usage of any prescribed medication during last 14 days and for OTC medicinal products, herbal products during the last 7 days preceding the first dosing.
- Any clinically significant illness during 3 months before screening.
- Participation in a drug research study/donation of blood within past 90 days.
- Consideration by the investigator, for any reason that the subject is an unsuitable candidate to receive study drug.

Analytical methods

The plasma samples of subjects were analyzed using LC/MS/MS method for Ambrisentan in Human Plasma using High Performance Liquid Chromatography Method with Tandem mass spectrometry over a Concentration range of 9.974 to 1595.838 ng/mL. The analytical method was developed and validated over a concentration range of 10.024 to 1603.814 ng/mL at the Bioanalytical laboratory of CRC, Mylan Laboratories Ltd.

A validation report of the analytical method entitled: "Determination of Ambrisentan in Human Plasma using Ultra Performance Liquid Chromatography Method with Tandem Mass Spectrometry "was submitted by the applicant.

Pharmacokinetic variables

As the objective of the study was to compare and evaluate the bioequivalence and characterize the pharmacokinetic profile of the test and reference formulations of Ambrisentan Tablets 10 mg to assess its bioequivalence and the following primary pharmacokinetic parameters were calculated:

Primary Variables: C_{max} and AUC_{0-t}

Secondary Variables: AUC_{0-inf}, T_{max} , $T_{1/2}$, Kel and $AUC\_\%Extrap\_obs$

Statistical methods

For pharmacokinetic and statistical analysis, actual time of blood sample collection was used for estimation of pharmacokinetic parameters, which was computed using non-compartmental model of Phoenix WinNonlin version 6.3.

Statistical analysis was performed on the data obtained assaying the ambrisentan concentration in the plasma samples collected, using SASR Software (Version 9.2).

Descriptive statistics of all the primary pharmacokinetic parameters were computed and reported for ambrisentan. The ln-transformed pharmacokinetic parameters C_{max} AUC_{0-t} and AUC_{0-inf} for ambrisentan were subjected to Analysis of Variance (ANOVA). ANOVA model was included Sequence, Formulation, Period and Subject (Sequence) as fixed effects. Sequence effect was tested using Subject (Sequence) as error term.

An F-test was performed to determine the statistical significance of the Formulation and Period effects involved in the model at a significance level of 5% (alpha= 0.05) and Sequence effect involved in the model at a significance level of 10% (alpha= 0.10).

Determination of sample size

The maximum observed intra-subject variability for Ambrisentan among primary pharmacokinetic parameters (Cmax) was found to be 22%. Hence, considering the CV of 23% the following estimates were considered for the computation of sample size:

T/R ratio (expected between) = 95-105.3%

Intra-Subject C.V (%) = 23%

Significance Level = 5%

Power = >90%

Bioequivalence Limit=80-125.00%

Based on the above estimates, a sample size of 32 subjects would be sufficient to establish bioequivalence between formulations with adequate power. To account for withdrawals and dropouts due to adverse events or non-compliance or due to personal reasons 36 subjects were randomized and dosed.

Results

Table 3. Pharmacokinetic parameters for Ambrisentan (non-transformed Mean values, Study C17139)

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-72h)}$	8624.866	1740.4036	8688.705	1967.4531
$AUC_{(0-\infty)}$	8904.053	1764.1561	9002.069	1991.2844
C_{max}	1313.281	236.5773	1293.649	271.4848
T_{max}*	1.25 (0.50-4.00)		1.25 (0.75-3.50)	
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours post dose			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Parameters (Units)	Un-transformed Data (Mean ± SD) n=35	
	Test Product (T)	Reference Product (R)
K_{el} (1/hr)	0.075±0.0139	0.075±0.0165
$t_{½}$ (hr)	9.539±1.9412	9.755±2.1985
AUC_%Extrap_obs(%)	3.173±1.8483	3.558±1.9556

The Summary Statistics of Pharmacokinetic Parameters of Ambrisentan for Test Product (T) and Reference Product (R) are presented in **Table 8**.

Table 4. Statistical analysis for Ambrisentan (ln-transformed values, Study C17139)

Product/Statistics		C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	AUC_{0-inf} (ng.hr/mL)
Test Product (T)				
N		35	35	35
Mean		1313.281	8624.866	8904.053
SD		236.5773	1740.4036	1764.1561
CV (%)		18.0	20.2	19.8
Geometric Mean		1292.517	8456.980	8735.718
Reference Product (R)				
N		35	35	35
Mean		1293.649	8688.705	9002.069
SD		271.4848	1967.4531	1991.2844
CV (%)		21.0	22.6	22.1
Geometric Mean		1267.418	8485.959	8800.864
Analysis of Variance p-value				
Ln-transformed	Formulation	0.5613	0.8202	0.5078
	Sequence	0.8594	0.4994	0.5557
	Period	0.0648	0.0063	0.0063
Geometric Least Squares Means				
Ln-transformed	Test (T)	1293.995	8466.687	8744.506
	Reference (R)	1266.319	8487.946	8802.469
Ratio of Geometric Least Squares Means (%) (T/R)				
Ln-transformed		102.19	99.75	99.34
Intra-subject CV (%)				
Ln-transformed		15.5	4.6	4.1
90% Confidence Interval (T vs.R)				
Ln-transformed	Lower Limit	96.01	97.92	97.70
	Upper Limit	108.76	101.61	101.01
Power (%)				
Ln-transformed		100.0	100.0	100.0

Safety data

Thirty six (36) subjects in period-1 and Thirty five (35) subjects in period-2 were administered with the study drug on 03 Aug 2017 and 10 Aug 2017 respectively with a washout period of 07 days between the dosing days as per the randomization schedule.

No AE's were reported during the study and in post study safety assessment. No SAEs and deaths were reported during the study and in post study safety assessment.

Additional safety data were submitted from two additional bioequivalence studies conducted for submissions to other regulatory authorities. In the first one (34 participants), four adverse events were

reported and all of them were possibly related to the study drug. Two adverse events were reported for one subject (increased eosinophils, increased ABS (eosinophils)) and two adverse events for another subject (increased SGOT, increased SGPT).

In the second BE study (48 participants) ten 10 AEs reported by six subjects over the course of the study. There was only one (1) AE (Headache) that was considered possibly related to the oral administration of Ambrisentan Mylan Tablets 10 mg.

Conclusions

Based on the presented bioequivalence study Ambrisentan Mylan is considered bioequivalent with Volibris.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

This is a generic application for the marketing authorisation of Ambrisentan 5 and 10 mg tablets which was supported by one bioequivalence study.

With regard to the bioequivalence study submitted by the Applicant, selection of PK parameters, determination of sample size, statistical evaluation of the PK parameters and the acceptance ranges for bioequivalence are in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**). The statistical methods chosen were considered appropriate.

Median range of the observed tmax was comparable between the two treatments. The t1/2 was also similar between the two treatments (9.53 hours for Ambrisentan Mylan and 9.75 hours for Volibris).

Based on the presented bioequivalence study Ambrisentan 10 mg tablets are considered bioequivalent with Volibris 10 mg tablets.

The applicant also requested a waiver for the *in vivo* bioequivalence study for the lowest strength of 5mg.

The two pharmaceutical products are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and the composition of the strengths are quantitatively proportional. The applicant also provided data for the two different srengths, which demonstrated that their corresponding dissolution profiles were similar in all dissolution media. Therefore, the request for waiver of the bio-study on the 5 mg was accepted by the CHMP.

2.4.6. Conclusions on clinical aspects

The application contains an adequate review of published clinical data and bioequivalence has been shown between Ambrisentan Mylan and Volibris 10 mg tablets based on the presented bioequivalence study.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Teratogenicity • Decreased haemoglobin, haematocrit, anaemia including anaemia requiring transfusion • Hepatotoxicity
Important potential risks	• Testicular tubular atrophy/male infertility
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance activities are sufficient to characterise the risks associated with ambrisentan use.

Risk minimisation measures

Safety concern	Risk minimisation measures
Teratogenicity	Routine risk minimization measures in SmPC sections 4.2, 4.3, 4.4, 4.6 and 5.3 and PL section 2 Additional risk minimisation measures Educational materials (Patient Reminder Card).
Decreased haemoglobin, haematocrit, anaemia including anaemia requiring transfusion	Routine risk minimization measures in SmPC sections 4.4, 4.8 and 5.1 and PL sections 2 and 4
Hepatotoxicity	Routine risk minimization measures in sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC and sections 2 and 4 of the PL Additional risk minimisation measures: Educational materials (Patient Reminder Card).
Testicular tubular atrophy/male infertility	Routine risk minimization measures in sections 4.6 and 5.3 of the SmPC and section 2 of the PL

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.

3. Benefit-risk balance

This application concerns a generic version of ambrisentan tablets. The reference product, Volibris, 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. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open-label, randomized, two-treatment, two-period, two-sequence, single-dose, crossover design in normal healthy adult male human subjects under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Ambrisentan Mylan met the protocol-defined criteria for bioequivalence when compared with Volibris. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ambrisentan Mylan is favourable in the following indication:

for the treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to use of Ambrisentan in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

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

- Patient reminder card
- Patient reminder card should include the following key elements:
    - That Ambrisentan Mylan is teratogenic in animals;
    - That pregnant women must not take Ambrisentan Mylan;
    - 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 Mylan may cause liver injury.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.