IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ambrisentan Rowex Limited 5 mg film-coated tablets
Ambrisentan
PA0711/306/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Ambrisentan Rowex Limited 5 mg & 10 mg film-coated tablets, from Rowex Ltd for the treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, and efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

The HPRA was RMS for this procedure, the procedure number of which was IE/H/1112/001-002/DC.

The active substance, ambrisentan, is licensed for supply under prescription only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website.

Name of the product	Ambrisentan Rowex Limited 5 mg film-coated tablets Ambrisentan Rowex Limited 10 mg film-coated tablets
Name(s) of the active substance(s) (INN)	ambrisentan
Pharmacotherapeutic classification (ATC code)	C02KX02
Pharmaceutical form and strength(s)	Film-coated tablet; 5 mg, 10 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA0711/306/001-002
Marketing Authorisation Holder	Rowex Ltd
MRP/DCP No.	IE/H/1106/001-002/DC
Reference Member State	IE
Concerned Member State	CZ EE IT LT LV

II. QUALITY ASPECTS

II.1. Introduction

This application is for Ambrisentan Rowex Limited 5 mg and 10 mg film-coated tablets.

II.2 Drug substance

The active substance is Ambrisentan, an established active substance not described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality of the active substance. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

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

P.3 Manufacture of the Product

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

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

P.4 Control of Other Substances (Excipients)

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

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

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

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

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

II.4 Discussion on Chemical and Pharmaceutical Aspects

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

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Volibris (ambrisentan) 10 mg Tablets on the European market since 2008. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. The overview provided based on literature review is thus appropriate. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

The ambrisentan PECsurfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.
Thus, it may be assumed that ambrisentan is unlikely to present a risk to the environment in normal conditions of use in the European markets. No further environmental risk assessment is considered necessary or justifiable, and no any special labelling warnings are deemed to be necessary.

III.3 Discussion on the non-clinical aspects

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

IV. CLINICAL ASPECTS

IV.1 Introduction

Ambrisentan is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Volibris marketed by Glaxo Operations UK Ltd., United Kingdom.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ambrisentan 10 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Volibris.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out.. Based on the pharmacokinetic parameters of active substance, the reference tablet and test tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 5mg film-coated tablets are dose proportional with the 10mg form. The pharmacokinetics of ambrisentan are dose-linear over a range of 1 to 100 mg. The results of the bioequivalence study performed with the 10mg film-coated tablet form therefore apply to the other strengths.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption
Ambrisentan is absorbed rapidly in humans. After oral administration, maximum plasma concentrations (Cmax) of ambrisentan typically occur around 1.5 hours post-dose under both fasted and fed conditions. Cmax and area under the plasma concentration-time curve (AUC) increase dose proportionally over the therapeutic dose range, and is dose-linear over a range of 1 to 100 mg. Steady-state is generally achieved following 4 days of repeat dosing.

A food-effect study involving administration of ambrisentan to healthy volunteers under fasting conditions and with a high-fat meal indicated that the Cmax was decreased 12% while the AUC remained unchanged. This decrease in peak concentration is not clinically significant, and therefore ambrisentan can be taken with or without food.

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

Biotransformation
Ambrisentan is a non-sulphonamide (propanoic acid) ERA. Ambrisentan is glucuronidated via several UGT isoenzymes (UGT1A9S, UGT2B7S and UGT1A3S) to form ambrisentan glucuronide (13%). Ambrisentan also undergoes oxidative metabolism mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19 to form 4-hydroxymethyl ambrisentan (21%) which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide (5%). The binding affinity of 4-hydroxymethyl ambrisentan for the human endothelin receptor is 65-fold less than ambrisentan. Therefore at concentrations observed in the plasma (approximately 4% relative to parent ambrisentan), 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

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

IV.3 Pharmacodynamics

Mechanism of action

Ambrisentan is an orally active, propanoic acid-class, ERA selective for the endothelin A (ET_A) receptor. Endothelin plays a significant role in the pathophysiology of PAH.
• Ambrisentan is a potent (Ki 0.016 nM) and highly selective ET_A antagonist (approximately 4000-fold more selective for ETA as compared to ET_B).
• Ambrisentan blocks the ET_A receptor subtype, localized predominantly on vascular smooth muscle cells and cardiac myocytes. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.
• The selectivity of ambrisentan for the ET_A over the ET_B receptor is expected to retain ET_B receptor mediated production of the vasodilators nitric oxide and prostacyclin.

Clinical efficacy and safety

Two randomised, double-blind, multi-centre, placebo controlled, Phase 3 pivotal studies were conducted (ARIES-1 and 2). ARIES-1 included 201 patients and compared ambrisentan 5 mg and 10 mg with placebo. ARIES-2 included 192 patients and compared ambrisentan 2.5 mg and 5 mg with placebo. In both studies, ambrisentan was added to patients' supportive/background medication, which could have included a combination of digoxin, anticoagulants, diuretics, oxygen and vasodilators (calcium channel blockers, ACE inhibitors). Patients enrolled had IPAH or PAH associated with connective tissue disease (PAH-CTD). The majority of patients had WHO functional Class II (38.4%) or Class III (55.0%) symptoms. Patients with pre-existent hepatic disease (cirrhosis or clinically significantly elevated aminotransferases) and patients using other targeted therapy for PAH (e.g. prostanoids) were excluded. Haemodynamic parameters were not assessed in these studies.

The primary endpoint defined for the Phase 3 studies was improvement in exercise capacity assessed by change from baseline in 6 minute walk distance (6MWD) at 12 weeks. In both studies, treatment with ambrisentan resulted in a significant improvement in 6MWD for each dose of ambrisentan.

The placebo-adjusted improvement in mean 6MWD at week 12 compared to baseline was 30.6 m (95% CI: 2.9 to 58.3; p=0.008) and 59.4 m (95% CI: 29.6 to 89.3; p<0.001) for the 5 mg group, in ARIES 1 and 2 respectively. The placebo-adjusted improvement in mean 6MWD at week 12 in patients in the 10 mg group in ARIES-1 was 51.4 m (95% CI: 26.6 to 76.2; p <0.001).

A pre-specified combined analysis of the Phase 3 studies (ARIES-C) was conducted. The placebo-adjusted mean improvement in 6MWD was 44.6 m (95% CI: 24.3 to 64.9; p<0.001) for the 5 mg dose, and 52.5 m (95% CI: 28.8 to 76.2; p<0.001) for the 10 mg dose.

In ARIES-2, ambrisentan (combined dose group) significantly delayed the time to clinical worsening of PAH compared to placebo (p<0.001), the hazard ratio demonstrated an 80% reduction (95% CI: 47% to 92%). The measure included: death, lung transplantation, hospitalisation for PAH, atrial septostomy, addition of other PAH therapeutic agents and early escape criteria. A statistically significant increase (3.41 ± 6.96) was observed for the combined dose group in the physical functioning scale of the SF-36 Health Survey compared with placebo (-0.20 ± 8.14, p=0.005). Treatment with ambrisentan led to a statistically significant improvement in Borg Dyspnea Index (BDI) at week 12 (placebo-adjusted BDI of -1.1 (95% CI: -1.8 to -0.4; p=0.019; combined dose group)).

Long term data

Patients enrolled into ARIES-1 and 2 were eligible to enter a long term open label extension study ARIES-E (n=383). The combined mean exposure was approximately 145 ± 80 weeks, and the maximum exposure was approximately 295 weeks. The main primary endpoints of this study were the incidence and severity of adverse events associated with long-term exposure to ambrisentan, including serum LFTs. The safety findings observed with long-term ambrisentan exposure in this study were generally consistent with those observed in the 12 week placebo-controlled studies.

The observed probability of survival for subjects receiving ambrisentan (combined ambrisentan dose group) at 1, 2 and 3 years was 93%, 85% and 79% respectively.

In an open label study (AMB222), ambrisentan was studied in 36 patients to evaluate the incidence of increased serum aminotransferase concentrations in patients who had previously discontinued other ERA therapy due to aminotransferase abnormalities. During a mean of 53 weeks of treatment with ambrisentan, none of the patients enrolled had a confirmed serum ALT >3xULN that required permanent discontinuation of treatment. Fifty percent of patients had increased from 5 mg to 10 mg ambrisentan during this time.

The cumulative incidence of serum aminotransferase abnormalities >3xULN in all Phase 2 and 3 studies (including respective open label extensions) was 17 of 483 subjects over a mean exposure duration of 79.5 weeks. This is an event rate of 2.3 events per 100 patient years of exposure for ambrisentan. In the ARIES-E open label long term extension study, the 2 year risk of developing serum aminotransferase elevations >3xULN in patients treated with ambrisentan was 3.9%.

Other clinical information

An improvement in haemodynamic parameters was observed in patients with PAH after 12 weeks (n=29) in a Phase 2 study (AMB220). Treatment with ambrisentan resulted in an increase in mean cardiac index, a decrease in mean pulmonary artery pressure, and a decrease in mean pulmonary vascular resistance.

Decrease in systolic and diastolic blood pressures has been reported with ambrisentan therapy. In placebo controlled clinical trials of 12 weeks duration mean reduction in systolic and diastolic blood pressures from base line to end of treatment were 3mm Hg and 4.2 mm Hg respectively. The mean decreases in systolic and diastolic blood pressures persisted for up to 4 years of treatment with ambrisentan in the long term open label ARIES E study.

No clinically meaningful effects on the pharmacokinetics of ambrisentan or sildenafil were seen during a drug-drug interaction study in healthy volunteers, and the combination was well tolerated. The number of patients who received concomitant ambrisentan and sildenafil in ARIES-E and AMB222 was 22 patients (5.7%) and 17 patients (47%), respectively. No additional safety concerns were identified in these patients.

Clinical efficacy in combination with tadalafil

A multicenter, double-blind, active comparator, event-driven, Phase 3 outcome study (AMB112565/AMBITION) was conducted to assess the efficacy of initial combination of ambrisentan and tadalafil vs. monotherapy of either ambrisentan or tadalafil alone, in 500 treatment naive PAH patients, randomised 2:1:1, respectively. No patients received placebo alone. The primary analysis was combination group vs. pooled monotherapy groups. Supportive comparisons of combination therapy group vs. the individual monotherapy groups were also made. Patients with significant anaemia, fluid retention or rare retinal diseases were excluded according to the investigators' criteria. Patients with ALT and AST values >2xULN at baseline were also excluded.

At baseline, 96% of patients were naive to any previous PAH-specific treatment, and the median time from diagnosis to entry into the study was 22 days. Patients started on ambrisentan 5 mg and tadalafil 20 mg, and were titrated to 40 mg tadalafil at week 4 and 10 mg ambrisentan at week 8, unless there were tolerability issues. The median double-blind treatment duration for combination therapy was greater than 1.5 years.

The primary endpoint was the time to first occurrence of a clinical failure event, defined as:
- death, or
- hospitalisation for worsening PAH,
- disease progression,
- unsatisfactory long-term clinical response.

The mean age of all patients was 54 years (SD 15; range 18–75 years of age). Patients WHO FC at baseline was II (31%) and FC III (69%). Idiopathic or heritable PAH was the most common aetiology in the study population (56%), followed by PAH due to connective tissue disorders (37%), PAH associated with drugs and toxins (3%), corrected simple congenital heart disease (2%), and HIV (2%). Patients with WHO FC II and III had a mean baseline 6MWD of 353 metres.

Outcome endpoints

Treatment with combination therapy resulted in a 50% risk reduction (hazard ratio [HR] 0.502; 95% CI: 0.348 to 0.724; p=0.0002) of the composite clinical failure endpoint up to final assessment visit when compared to the pooled monotherapy group [Figure 1 and Table 1]. The treatment effect was driven by a 63% reduction in hospitalisations on combination therapy, was established early and was sustained. Efficacy of combination therapy on the primary endpoint was consistent on the comparison to individual monotherapy and across the subgroups of age, ethnic origin, geographical region and aetiology (iPAH /hPAH and PAH-CTD). The effect was significant for both FC II and FC III patients.

Figure 1

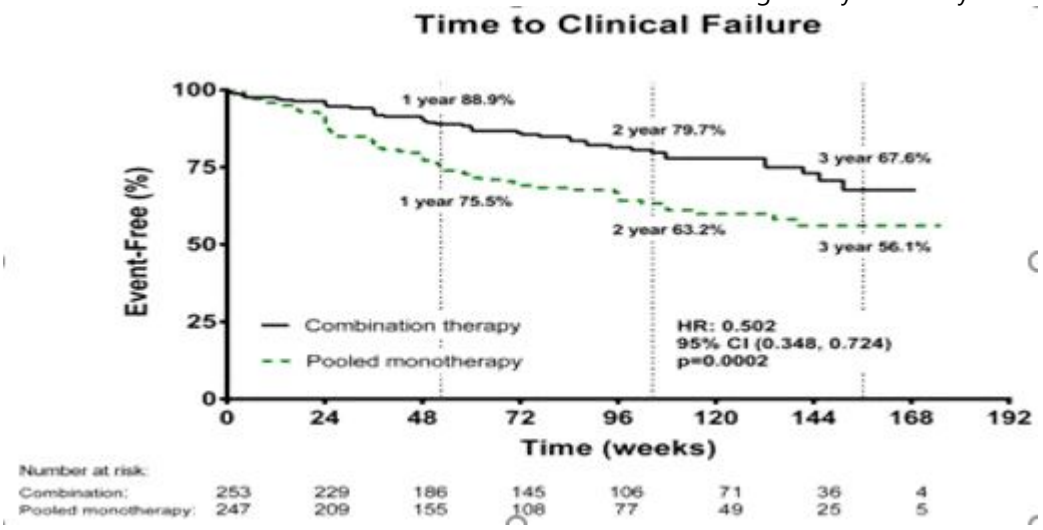

Table 1

	Ambrisentan + Tadalafil (N=253)	**Monotherapy Pooled (N=247)**	**Ambrisentan monotherapy (N=126)**	**Tadalafil monotherapy (N=121)**
Time to First Clinical Failure Event (Adjudicated)				
Clinical failure, no. (%)	46 (18%)	77 (31%)	43 (34%)	34 (28%)
Hazard ratio (95% CI)		0.502 (0.348, 0.724)	0.477 (0.314, 0.723)	0.528 (0.338, 0.827)
P-value, Log-rank test		0.0002	0.0004	0.0045
Component as First Clinical Failure Event (Adjudicated)				
Death (all-cause)	9 (4%)	8 (3%)	2 (2%)	6 (5%)
Hospitalisation for worsening PAH	10 (4%)	30 (12%)	18 (14%)	12 (10%)
Disease progression	10 (4%)	16 (6%)	12 (10%)	4 (3%)
Unsatisfactory long-term clinical response	17 (7%)	23 (9%)	11 (9%)	12 (10%)
Time to First Hospitalisation for Worsening PAH (Adjudicated)				
First hospitalisation, no. (%)	19 (8%)	44 (18%)	27 (21%)	17 (14%)
Hazard ratio (95% CI)		0.372	0.323	0.442
P-value, Log-rank test		0.0002	<0.0001	0.0124

Secondary endpoints

Secondary endpoints were tested:

Table 2

Secondary Endpoints (change from baseline to week 24)	**Ambrisentan + Tadalafil**	**Monotherapy pooled**	Difference Confidence Interval	P value
NT-proBNP (% reduction)	-67.2	-50.4	% difference -33.8; 95% CI: -44.8, -20.7	p<0.0001
% subjects achieving a satisfactory clinical	39	29	Odds ratio 1.56; 95% CI:	p=0.026

response at week 24			1.05, 2.32	
6MWD (metres, median change)	49.0	23.8	22.75m; 95% CI: 12.00, 33.50	p<0.0001

Idiopathic Pulmonary Fibrosis

A study of 492 patients (ambrisentan N=329, placebo N=163) with idiopathic pulmonary fibrosis (IPF), 11% of which had secondary pulmonary hypertension (WHO group 3), has been conducted, but was terminated early when it was determined that the primary efficacy endpoint could not be met (ARTEMIS-IPF study). Ninety events (27%) of IPF progression (including respiratory hospitalisations) or death were observed in the ambrisentan group compared to 28 events (17%) in the placebo group. Ambrisentan is therefore contraindicated for patients with IPF with or without secondary pulmonary hypertension.

IV.4 Clinical Efficacy

The clinical efficacy of ambrisentan is well characterised.

IV.5 Clinical Safety

The clinical safety of ambrisentan is well characterised.

Risk Management Plan

The applicant 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 5mg and 10mg film coated tablets.

Summary of safety concerns

Important identified risks	Teratogenicity Decreased hemoglobin/ hematocrit, anemia including anemia requiring transfusion Hepatotoxicity
Important potential risks	Testicular tubular atrophy/ Male infertility
Missing information	None

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Additional risk minimisation measures in the form of a patient reminder card to address the safety concerns of teratogenicity and hepatotoxicity are proposed by the applicant, which is endorsed.

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

SAs this is a generic application in accordance with Directive 2001.83/EC, the need for repetitive texts can be avoided. The applicant has presented details of a well-conducted bioequivalence study which has shown equivalence between their product and the reference product. Following on from this, equivalent efficacy and safety is also inferred,

V. OVERALL CONCLUSIONS

Ambrisentan Rowex Limited 5mg & 10mg Film-coated Tablets are generic forms of Volibris, is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

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

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

The HPRA, on the basis of the data submitted considered that Ambrisentan Rowex Limited 5mg & 10mg Film-coated Tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

15.07.2026