LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ambrisentan Bluefish (ambrisentan)

SE/H/1981/01-02/DC

This module reflects the scientific discussion for the approval of Ambrisentan Bluefish. The procedure was finalised on 2021-09-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Ambrisentan Bluefish, 5 mg and 10 mg, film-coated tablet.

The active substance is ambrisentan. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Ambrisentan Bluefish, 5 mg and 10 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Bluefish Pharmaceuticals AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, FR and ES as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Volibris, 5 mg and 10 mg, film-coated tablet, authorised in the Union since 2008, with GlaxoSmithKline (Ireland) Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Volibris, 10 mg, film-coated tablet, from IT with GlaxoSmithKline (Ireland) Limited as marketing authorisation holder.

Potential similarity with orphan medicinal products

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Ambrisentan Bluefish is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Adempas and Opsumit.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Adempas and Opsumit in the treatment of PAH, does not prevent the granting of the marketing authorisation of Ambrisentan Bluefish. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of Ambrisentan are well known. As Ambrisentan is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Ambrisentan Bluefish is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Ambrisentan Bluefish from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one pivotal bioequivalence study comparing Ambrisentan with the reference product Volibris.

Pharmacokinetic properties of the active substance
Absorption: Ambrisentan is absorbed rapidly in humans. After oral administration, maximum plasma concentrations (C_{max}) of ambrisentan typically occur around 1.5 hours post-dose under both fasted and fed conditions.

A food-effect study involving administration of ambrisentan to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} 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.

Linearity: C_{max} and area under the plasma concentration-time curve (AUC) increase dose proportionally over the therapeutic dose range.

Elimination: Plasma elimination half-life in humans ranges from 13.6 to 16.5 hours.

Study Code: AMB-T1217/65
Methods
This was a single-dose, two-way crossover study conducted in 30 healthy volunteers (27 completed), comparing Ambrisentan, 10 mg, film-coated tablet with Volibris, 10 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of ambrisentan were determined with an LC-MS/MS

method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 15 January 2018 and 02 February 2018.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for ambrisentan, n=27.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**7119.0 ± 2303.58**	**938.678 ± 184.74**	**1.33 (0.50 - 2.50)**
Reference	**7052.7 ± 2158.39**	**888.989 ± 170.35**	**1.33 (0.50 - 3.00)**
***Ratio (90% CI)**	**100.42 (96.48-104.52)**	**106.09 (98.35-114.44)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 5 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strength of 5 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of ambrisentan is linear between 5 mg and 10 mg.

Based on the submitted bioequivalence study, Ambrisentan Bluefish is considered bioequivalent with Volibris.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Bluefish.

The submitted Risk Management Plan, version 1.3 signed 2021-09-07 is considered acceptable.

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

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Teratogenicity	Routine risk minimisation measures: Information is included in Sections 4.2, 4.3, 4.4, 4.6 and 5.3 of the EU SmPC PL Section 2 Limited package supply Prescription only medicine Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Questionnaire (pregnancy report form) Additional pharmacovigilance activities: None
Decreased haemoglobin, haematocrit, anaemia including anaemia requiring transfusion	Routine risk minimisation measures: Information is included in Sections 4.4, 4.8 and 5.1 of the EU SmPC PL Section 2 and 4 Limited package supply Prescription only medicine Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Hepatotoxicity	Routine risk minimisation measures: Information is included in Sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the EU SmPC PL Section 2 and 4 Limited package supply Prescription only medicine Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Testicular tubular atrophy/male infertility	Routine risk minimisation measures: Information is included in Sections 4.6 and 5.3 of the EU SmPC PL Section 2 Limited package supply Prescription only medicine Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Additional risk minimisation activities have been included in the table:
Specific adverse reaction follow-up questionnaires have been prepared for the safety concerns
-Teratogenicity

-Anaemia, decreased haemoglobin, haematocrit
-Hepatotoxicity
-Testicular tubular atrophy/male infertility

Additional Risk minimisation measures (Patient reminder Card)

Draft key message in the Patient Reminder Card

This Patient Reminder Card is intended to minimise the risks identified in the frame of the European risk management plan established for Ambrisentan Bluefish.

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.

The additional risk minimisation measures submitted in the Risk Management Plan, version 1.3 signed 2021-09-07 are considered acceptable.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to (content) Volibris, EMEA/H/C/000839, (layout) Venlafaxine Bluefish leaflet, UK/H/1400/01-03/DC (transferred to SE/H/1870/01-03/DC after Brexit). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Ambrisentan Bluefish, is found adequate. There are no objections to approval of Ambrisentan Bluefish, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

Additional risk minimisation measures (including educational material)
This medicine has additional risk minimisation measures for the following risks: Teratogenicity and

Hepatotoxicity. The additional risk minimisation measures consist of Educational material for patients (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.

VII. APPROVAL

The decentralised procedure for Ambrisentan Bluefish, 5 mg and 10 mg, film-coated tablet was positively finalised on 20210922.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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