LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Macitentan Bioglan
(macitentan)

SE/H/2665/01/DC

This module reflects the scientific discussion for the approval of Macitentan Bioglan. The procedure was finalised at 2025-09-11. 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, the Member States have agreed to grant a marketing authorisation for Macitentan Bioglan., 10 mg, Film-coated tablet.

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

II. EXECUTIVE SUMMARY

II.1 About the product

Endothelin (ET)-1 and its receptors (ET_A and ET_B) mediate a variety of effects such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.

Macitentan is an orally active potent endothelin receptor antagonist, active on both ET_A and ET_B receptors and approximately 100-fold more selective for ET_A as compared to ET_B *in vitro*. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.

Pharmacotherapeutic group: anti-hypertensives, anti-hypertensives for pulmonary arterial hypertension. ATC code: C02KX04

II.2 General comments on the submitted dossier

The application for Macitentan Bioglan, 10 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following countries as concerned member states (CMS):

- SE/H/2665 – ES and IT

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Opsumit, 10 mg, film-coated tablet, authorised in EU since 2013, with Janssen-Cilag International N.V. as marketing authorisation holder.

The reference product used in the bioequivalence study is Opsumit, 10 mg, film-coated tablet, from Germany with Janssen-Cilag International N.V. 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, Macitentan Bioglan is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to the authorised orphan medicinal products listed in Table 1 above.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for these products do not prevent the granting of the marketing authorisation of Macitentan

Bioglan. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted study has been provided. The clinical and the bioanalytical facilities were inspected by the Spanish authority in 2019, with critical findings. The impact of the critical and major findings observed on the trial inspected was evaluated by the inspection team and found that the subject well-being and data produced were not comprised. Further, the clinical and the bioanalytical facilities were inspected by the US-FDA in 2020, without any critical findings. No issues regarding GCP have been identified during the assessment of the submitted bioequivalence study. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of macitentan are well known. As macitentan is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

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

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Macitentan Bioglan (Macitentan) with the reference product Opsumit.

Pharmacokinetic properties of the active substance
Absorption:
Maximum plasma concentrations of macitentan are achieved about 8 hours after administration. Thereafter, plasma concentrations of macitentan and its active metabolite aprocitentan decrease slowly, with an apparent elimination half-life of approximately 16 hours and 48 hours, respectively.

In healthy subjects, the exposure to macitentan and its active metabolite is unchanged in the presence of food and, therefore, macitentan may be taken with or without food.

Study (MACI23040)
Methods
This was a single-dose, two-way crossover study conducted in 32 healthy volunteers (23 completed), comparing Macitentan, 10 mg, film-coated tablet with Opsumit, 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 macitentan and active metabolite aprocitentan were determined with LC-MS/MS methods. Data for aprocitentan was provided as supporting information only. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-72} and C_{max}. The study was conducted between 07/08/2023 and 31/08/2023.

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 macitentan, n=23.

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**4829.214 ± 1164.893**	**160.317 ± 46.255**	**8.67 (7.00-36.00)**
Reference	**5133.957 ± 1353.394**	**172.148 ± 40.544**	**8.00 (4.00-12.00)**
***Ratio (90% CI)**	**94.38 (89.07-100.01)**	**91.18 (81.79-101.66)**	**-**

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-72} 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%.

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**). Evaluation of bioequivalence is based upon measured concentrations of the parent compound macitentan. Data for the active metabolite aprocitentan was provided as supporting information only. The bioanalytical method was adequately validated.

Based on the submitted bioequivalence study, Macitentan Bioglan is considered bioequivalent with Opsumit.

Pharmacodynamics/Clinical efficacy/Clinical safety

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

Pharmacovigilance system

Proposed MAH: Bioglan AB (RMS), Reig Jofre (CMS ES and IT)

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 the product.

Part II Safety specification

Summary of safety concerns	
Important identified risks	• Hepatotoxicity • Teratogenicity
Important potential risks	• None
Missing information	• None

The safety specification is aligned with current version safety specification of the reference product and is thus endorsed.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant. However, in accordance with the reference product, follow-up questionnaire for teratogenicity is proposed, which is endorsed.

Part V Risk minimisation measures
In addition to Routine risk minimisation the applicant suggests an additional risk minimisation activity in the form of a **patient card,** informing patients on the important identified risks: **teratogenicity and hepatoxicity**.
The patient card is provided in every package and aimed at every patient using the product.
This is in line with the reference product, and the additional risk minimisation measure is endorsed.

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	Routine risk minimisation measures: – ***SmPC***: Sections 4.3, 4.4 and 4.8 – ***PIL***: Sections 2 and 4 – ***Legal status***: Prescription only medicine Additional risk minimisation measures: – Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: – None Additional pharmacovigilance activities – None
Teratogenicity	Routine risk minimisation measures: – ***SmPC***: Sections 4.3, 4.4 and 4.6 – ***PIL***: Section 2 – ***Legal status***: Prescription only medicine	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: – Patient card	– Specific adverse reaction follow-up questionnaire for teratogenicity Additional pharmacovigilance activities – None

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment:

- SE/H/2665/01/DC: The submitted Risk Management Plan **version 1.1 dated 22-07-2025** is acceptable.

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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- 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. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Macitentan Bioglan, is found adequate. There are no objections to approval of Macitentan Bioglan., 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 benefit/risk is considered positive, and the application is therefore recommended for approval.

Please refer to section V.2 for information about the condition regarding Patient Card.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

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

  - Patient Card.
    The Patient Card is aimed at increasing awareness about the identified risks of teratogenicity and hepatotoxicity during treatment with Macitentan Bioglan.

  The Patient Card for patients prescribed Macitentan Bioglan should include the following key elements:
  - That the product is teratogenic in animals;
  - That pregnant women must not take the product
  - That women of childbearing potential must use reliable contraception;

- The need for monthly pregnancy tests;
- The need for regular monitoring of liver function because the product has hepatotoxic potential.

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

Full user test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The results 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.

Bridging of format
The full user test was performed with a leaflet of dimensions 180 x 720 mm (double-sided), and a bridging to a leaflet of dimensions 180 x 420 mm (double-sided) has been provided.
The bridging of leaflet format has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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