IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Opsaren 10 mg Film-coated Tablets
Macitentan
PA22865/018/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Opsaren 10 mg film-coated tablets, from Renata Pharmaceuticals (Ireland) Limited, 12 Crowe Street, Dundalk, Co. Louth, A91 NN29, Ireland on 06th February 2026 for the treatment of the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

This decentralised application concerns a generic version of Macitentan, under Opsaren trade name and is being submitted as a generic application under Article 10(1) of Directive 2001/82/EC as amended. Ireland is the reference member state with Denmark, Germany, France, Malta, Portugal, Sweden, Norway, Finland as concerned member states.

The legal status in Ireland is subject to medical prescription which may not be renewed and product is on restricted prescription.

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

Name of the product	Opsaren 10 mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Macitentan
Pharmacotherapeutic classification (ATC Code)	C02KX04
Pharmaceutical form and strength(s)	10 mg film coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/018/001
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited 12 Crowe Street Dundalk Co. Louth A91 NN29 Ireland
MRP/DCP No.	IE/H/1309/001
Reference Member State	IE
Concerned Member State(s)	DE, DK, FI, FR, MT, NO, PT, SE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Opsaren 10 mg Film-coated Tablets.

II.2 Drug substance

The active substance macitentan is an established active substance and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. 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 and ICH guidelines, and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

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 film-coated 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(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 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 relevant Ph. Eur. requirements and EU legislation for use with foodstuffs.

P.7 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, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation have been provided, assuring consistent quality of Opsaran 10 mg Film-coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Opsumit on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Opsaren 10 mg Film-coated Tablets is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Macitentan are well known. As Macitentan is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under article 10(1) of Directive 2001/83/EC.

Macitentan 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 Opsumit marketed by Janssen Pharmaceutica.

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

A single dose, open label, randomised, two-period, two-treatment, two-sequence, crossover, balanced, bioequivalence study was carried out.

Opsaren 10 mg film-coated tablets manufactured by Renata PLC, Dhaka Bangldesh was compared to the reference product Opsumit (Macitentan 10 mg film-coated tablets) manufactured by Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beers, Belgium.
Based on the pharmacokinetic parameters of the 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.

Bioequivalence was determined by a statistical comparison of Cmax and AUC_t for the test and reference products.

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

IV.2 Pharmacokinetics

A pharmacokinetic bioequivalence study was conducted as an open-label, randomised, balanced, two-treatment, two-period, two-sequence, single-dose crossover study in healthy adult subjects under fasting conditions.

The study compared the test and reference formulations, with bioequivalence assessed using Cmax and AUCt.

Opsaren met the bioequivalence criteria.

IV.3 Pharmacodynamics

No new studies were performed or required for this Article 10(1) generic application.

IV.4 Clinical Efficacy

No new studies were performed or required for this Article 10(1) generic application.

IV.5 Clinical Safety

As the active substance is a widely used, well-known substance, the applicant has not provided additional safety studies and further studies are not required.

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 Opsaren 10 mg film-coated tablets.

Safety specification

Summary of safety concerns	
Important identified risks	Hepatotoxicity Teratogenicity
Important potential risks	None
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:

Important Identified Risk Hepatotoxicity	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3 contraindication SmPC sections 4.4, Special warnings, and precautions for use SmPC sections 4.8. Undesirable effects PL section 2 and 4. Instructions for liver function monitoring and actions to be taken in case of elevated hepatic enzymes are provided in SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient alert card
Important Identified Risk: Teratogenicity	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3 contraindication SmPC sections 4.4, Special warnings, and precautions for use SmPC sections 4.6 Fertility, Pregnancy, and lactation PL section 2. Instructions for the use of Opsaren in women of childbearing potential and recommendation for monthly pregnancy tests during treatment are provided in SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient alert card

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.

IV.6 Discussion on the clinical aspects

Discussion of clinical aspects has been provided in IV.1 – IV.6 above.

V. OVERALL CONCLUSIONS

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Opsaren 10 mg film-coated tablets are generic forms of Opsumit 10 mg film-coated tablets. Opsumit is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence for Opsaren 10 mg film-coated tablets has been shown to comply with CHMP guidance documents.

The SmPC, Patient Leaflet and labelling are satisfactory, in line with current guidelines and 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 Opsaren 10 mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.