COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Macitentan Teva 10 mg, film-coated tablets (macitentan)

NL/H/5720/001/DC

Date: 22 April 2026

This module reflects the scientific discussion for the approval of Macitentan Teva 10 mg, film-coated tablets. The procedure was finalised on 9 April 2025. For information on changes after this date, please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ASMF	Active Substance Master File
BE	Bioequivalence
CBG /MEB	College ter Beoordeling van Geneesmiddelen /The Medicines Evaluation Board
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State(s)
DCP	Decentralised Procedure
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
LALA	Locally applied, locally acting products
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
PAH	Pulmonary Arterial Hypertension
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package Leaflet
PSURs	Periodic safety update reports
QC	Quality control
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary

Note: Not all abbreviations may apply for this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Macitentan Teva 10 mg, film-coated tablets, from Teva Nederland B.V.

The product is indicated for:
Adults
The product, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

Paediatric population
The product, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged less than 18 years and bodyweight ≥40 kg with WHO Functional Class (FC) II to III.

A comprehensive description of the up-to-date indications and posology is given in the SPC.

II. EXECUTIVE SUMMARY

II.1 Rationale for the product

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Opsumit 10 mg, film-coated tablets, which has been registered in the EEA via a centralised procedure EU/1/13/893 by Janssen-Cilag International NV since 20 December 2013.

This application has been assessed with The Netherlands as Reference Member State and CMS countries Austria, Belgium, Bulgaria, Croatia, Czechia, Denmark, Germany, Hungary, Iceland, Ireland, Italy, Luxembourg, Norway, Poland, Portugal, Romania, Slovakia, Spain, and Sweden as concerned member states (CMS).

Assessment of similarity with authorised orphan medicinal product(s) under market exclusivity
According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. Therefore, the MAH has provided a similarity assessment between Macitentan Teva and the current orphan product authorised in the EU. This orphan product and its indication is:
Winrevair (which obtained orphan market exclusivity on 27 August 2024, based on designation EU/3/20/2369), in combination with other pulmonary arterial hypertension (PAH)

therapies, is indicated for the treatment of PAH in adult patients with WHO Functional Class (FC) II to III, to improve exercise capacity.

The assessment included the comparison of the therapeutic indication, active substance, mechanism of action and principal (molecular) structure. After consideration of the MAH arguments, Macitentan Teva is not considered similar to the orphan product with regard to the therapeutic indication (as defined in Article 3 of Commission Regulation (EC) No. 847/2000). Therefore, the existence of any market exclusivity for Winrevair, in the treatment of PAH in adult patients with WHO Functional Class (FC) II to III, does not prevent the granting of the marketing authorisation for Macitentan Teva.

II.2 About the product

Endothelin (ET)-1 and its receptors (ETA and ETB) 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 ETA and ETB receptors and approximately 100-fold more selective for ETA as compared to ETB *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.

III. QUALITY ASPECTS

III.1 Introduction

Mactitentan Teva is a white, round film-coated tablet, debossed with “TV” on one side and “J7” on the other side. Each film-coated tablet contains 10 mg macitentan as active substance.

The excipients are:
Tablet core – mannitol, microcrystalline cellulose, povidone K-30, sodium starch glycolate (type A), and magnesium stearate.
Film-coating – poly (vinyl alcohol) (E1203), titanium dioxide (E171), PEG 3350 (E1521), and talc (E533b).

The film-coated tablets are either packed in polyvinyl chloride/polyvinylidene chloride/Aluminium (PVC/PVdC/Alu) blisters or perforated unit dose blisters, or in a high-density polyethylene (HDPE) bottle with polypropylene child-resistant cap and 2 units of silica gel desiccant.

III.2 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described. The active substance is macitentan, an established active substance not described in the European Pharmacopoeia. The active substance is a white to off-white powder and is insoluble in water. The polymorphic form of the active substance is routinely controlled.

An Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process comprises three linear chemical stages with three chemical transformations as defined in ICH Q11, as well as a final purification stage. The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Quality control of the drug substance

The drug substance specification includes relevant tests, additional specifications for particle size distribution and polymorphism, and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated. The active substance specification is considered adequate to control the quality and meets the requirements of various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of the drug substance

Stability data on the active substance have been provided for three batches in accordance with the applicable European guidelines. Based on the data submitted, the re-test period for the drug substances was confirmed for 60 months when stored under the stated conditions. This is acceptable.

III.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of the excipients is justified, and their functions explained.

Comparative dissolution at 3 pHs has been studied in support of bioequivalence. The QC dissolution method has been sufficiently justified.

Manufacturing process
The manufacturing process has been sufficiently described and critical steps identified. The manufacturing process has been validated according to relevant European/ICH guidelines.
An acceptable process validation scheme is provided for the manufacture on three consecutive product scale batches.

Control of excipients
The excipients comply with the current version of the Ph.Eur. monograph. With additional in-house specifications for film-coating solution. These specifications are acceptable.

Quality control of the drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description/appearance (including, dimensions), identity, dissolution, assay, content uniformity, degradation products, water content, and microbiology. Limits in the specification have been justified and are considered appropriate for the adequate quality control of the product.

An adequate risk evaluation report on nitrosamines has been submitted. No risk for the presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the non-compendial analytical methods have been provided. Batch analytical data for three batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of the drug product
Stability data on the product have been provided for three batches stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Furthermore, photostability studies were performed in accordance with ICH recommendations. The product is photostable. Based on the data submitted, a shelf life was granted of 36 months. The labelled storage conditions for the blisters are: “Store below 30°C”. The HDPE-bottles do not have any storage conditions.

In-use stability data have been provided demonstrating that the product remains stable for 60 days following first opening of the HDPE-container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

III.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Macitentan Teva has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

IV. NON-CLINICAL ASPECTS

IV.1 Ecotoxicity/environmental risk assessment (ERA)

Since Macitentan Teva is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

IV.2 Discussion on the non-clinical aspects

This product is a generic formulation of Opsumit which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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. Therefore, the member states agreed that no further non-clinical studies are required.

V. CLINICAL ASPECTS

V.1 Introduction

Macitentan is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

V.2 Pharmacokinetics

The MAH conducted one bioequivalence study in which the pharmacokinetic profile of the test product Macitentan Teva 10 mg, film-coated tablets (Teva Nederland B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Opsumit 10 mg, film-coated tablets (Janssen-Cilag International NV, Belgium).

The choice of the reference product in the bioequivalence study has been approved via CP.

Bioequivalence study

Study 4781/17

Design

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects,

aged 20-42 years. Each subject received a single dose (10 mg) of one of the two macitentan formulations. The tablet was orally administered with 240 mL water after a 10 hour fasting period. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 2, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 14, 16, 20, 24, 36, 48, 60 and 72 hours after administration of the products.

The design of the study is acceptable. According to the SPC, the product should be administered by swallowing the film-coated tablets whole, with water. They may be taken with or without food.

Fasted condition
Macitentan may be administered without reference to food intake. From the literature it is known that food does not interact with the absorption of macitentan. Therefore, a study under fed conditions is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject was withdrawn from the study (excluded from the pharmacokinetic analysis) because he did not check-in for period 2. The remaining 35 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of macitentan, 10 mg under fasted conditions.

Treatment N=35	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	6950 ± 1999	7589 ± 2707	256 ± 60	11.00 (4.00 – 12.50)
Reference (comparative Bioavailability data)	6525 ± 2055	7213 ± 3064	240 ± 51	9.50 (7.00 – 12.50)
***Ratio (90% CI)**	1.07 (1.04 – 1.10)	1.07 (1.04 – 1.10)	1.06 (1.02 – 1.11)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Macitentan Teva 10 mg is considered bioequivalent with Opsumit 10 mg.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

V.3 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 Macitentan Teva. At the time of approval, the most recent version of the RMP was version 1.2 with sign date off 6 February 2025.

Table 2. Summary table of safety concerns as approved in the RMP

Important identified risks	• Hepatoxicity • Teratogenicity
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities are sufficient for the risks and areas of missing information. In addition to the routine risk minimisation measures, the MAH shall ensure that in each Member State where Macitentan Teva is marketed, all patients who are expected to use Macitentan Teva 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 Teva.
The Patient Card for patients prescribed Macitentan Teva should include the following key elements:

- That Macitentan Teva is teratogenic in animals;
- That pregnant women must not take Macitentan Teva;
- That women of childbearing potential must use reliable contraception;
- The need for monthly pregnancy tests;
- The need for regular monitoring of liver function because Macitentan Teva has hepatotoxic potential.

V.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Opsumit. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

VI. USER CONSULTATION

The package leaflet (PL) 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.

A user consultation with target patient groups on the package leaflet (PL) has been performed based on a bridging report making reference to Opsumit 10 mg, film-coated tablets (EU/1/13/893/001) for key massages and content, and to Budesonide Teva 3 mg gastro-resistant capsules, hard (SE/H/2121/001/DC) for layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Macitentan Teva 10 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Opsumit 10 mg, film-coated tablets. Opsumit is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, based on the data submitted, considered that essential similarity has been demonstrated for Macitentan Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 April 2025.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5720/001/IB/001/G	Change in the name and/or address of a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier) Changes in the manufacturing process of the active substance - Minor change to the restricted part of an Active Substance Master File. Updates to ASMF	No	13-3-2026	Approved	N.A.
NL/H/5720/001/IA/002	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process.	No	16-3-2026	Approved	N.A.