COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Macitentan STADA Arzneimittel AG 10 mg, film-coated tablets (macitentan)

NL/H/6055/001/DC

Date: 5 August 2025

This module reflects the scientific discussion for the approval of Macitentan STADA Arzneimittel AG 10 mg, film-coated tablets. The procedure was finalised on 4 July 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

ASMF	Active Substance Master File
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
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
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Macitentan STADA Arzneimittel AG 10 mg, film-coated tablets, from Stada Arzneimittel AG.

The product is indicated for:
Adults
Macitentan STADA Arzneimittel AG, 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 (see section 5.1 of SmPC).

Paediatric population
Macitentan STADA Arzneimittel AG, 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 (see section 5.1 of SmPC).

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

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 tablet, which has been registered in the EEA via a centralised procedure (EU/1/13/893) since 20 December 2013.

The concerned member state (CMS) involved in this procedure was Germany.

Similarity assessment
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. A similarity assessment has been performed between Macitentan STADA Arzneimittel AG and Winrevair, which obtained orphan market exclusivity on 27 August 2024, based on designation EU/3/20/2369. The similarity assessment report was completed in 2024, concluding the two products were not similar and that with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Winrevair in the treatment of pulmonary arterial hypertension, does not prevent the granting of the marketing authorisation of Macitentan STADA Arzneimittel AG 10 mg film-coated tablets.

II. QUALITY ASPECTS

II.1 Introduction

Macitentan STADA Arzneimittel AG is a white to off-white, round, biconvex film-coated tablet and contains as active substance 10 mg of macitentan.

The excipients are:
Tablet core: maltodextrin (E1400), polysorbate 80 (E433), mannitol (E421), pregelatinised starch (maize starch), croscarmellose sodium (E468) and magnesium stearate (E572).
Film-coating: poly(vinyl alcohol) (E1203), talc (E553b), titanium dioxide (E171), glycerol monocaprylocaprate type I and sodium laurilsulfate (E487).

The film-coated tablets are packed in polyvinyl chloride/polyethylene/polyvinylidene chloride-Aluminium (PVC/PE/PVdC-Al) blisters.

II.2 Drug Substance

The active substance is macitentan, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off-white powder and is insoluble in water. For this product, polymorphic form I is routinely controlled.

Two Active Substance Master File (ASMF) procedures are 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
Both ASMF-holders
The manufacturing process consists of three linear chemical stages with three chemical transformations as defined in ICH Q11, as well as a final purification (crystallisation) stage. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for two batches by ASMF-holder 1 and one batch by ASMF-holder 2.

Stability of drug substance
Stability data on the active substance have been provided for three batches by each ASMF-holder in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of 60 months when stored under the stated conditions.

II.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 main development studies performed were the characterization of the reference products and several development trials to select the manufacturing process and excipients. The QC dissolution method has been sufficiently justified. Comparative dissolution at three pHs has been successfully studied in support of bioequivalence.

Manufacturing process
The product is manufactured by a wet granulation process which consists of blending, granulation, final blending, compression and film-coating. The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients, except for the coating material, comply with Ph.Eur. requirements. These specifications are acceptable. In-house specifications, provided for coating material are acceptable as well.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mas, identity, content uniformity, assay, related substances, microbiology and dissolution. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three production scaled batches stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies showed that the product is stable when exposed

to light. On basis of the data submitted, a shelf life was granted of 48 months. No specific storage conditions needed to be included in the SmPC or on the label.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Macitentan STADA Arzneimittel AG 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.

III.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.

IV. CLINICAL ASPECTS

IV.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.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Macitentan STADA Arzneimittel AG 10 mg, film-coated tablets (Stada Arzneimittel AG, Germany) 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 justified by comparison of dissolution study results and composition (at pH 1.0, 4.5 and 6.8). The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-center, open-label, single-dose, randomised, bioanalytical laboratory-blinded, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male (18) and female (6) subjects, aged 28-60 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 an overnight fasting period of at least 10 hours. Fasting continued for at least 4 hours following drug administration, after which a standardized lunch was served. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Macitentan may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of macitentan. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 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

All 24 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=24	**AUC_{0-t} (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	6166 (±1472)	223.5 (±48)	9.50 (7.00 – 10.03)
Reference	5806 (±1228)	207.8 (±49)	10.00 (8.00 – 10.02)
***Ratio (90% CI)**	1.06 (1.02 – 1.10)	1.08 (1.04 – 1.12)	-

AUC_{0-t}	Area under the plasma concentration-time curve from time zero to / 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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Macitentan STADA Arzneimittel AG 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).

IV.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 STADA Arzneimittel AG.

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

Important identified risks	Hepatotoxicity Teratogenicity
Important potential risks	None
Missing information	None

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

- Patient Card.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.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.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Opsumit 10 mg, film-coated tablets (EMEA/H/C/002697/0000) for content and Pirfenidon STADA 267 mg, film-coated tablets and Equitor 267 mg, film-coated tablets (DE/H/7079-7081/1-3/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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Macitentan STADA Arzneimittel AG 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, on the basis of the data submitted, considered that essential similarity has been demonstrated for Macitentan STADA Arzneimittel AG with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 July 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
-	-	-	-	-	-