EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2025
EMA/CHMP/216790/2025 Corr.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Macitentan Accord

International non-proprietary name: macitentan

Procedure No. EMEA/H/C/006524/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ANOVA	Analysis of variance
AP	Applicant's Part of an ASMF
API	Active Pharmaceutical Ingredient=active substance
AR	Assessment Report
AS	active substance= API
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AUC	Area under the curve
BE	Bioequivalence
CC	Calibration curve
CEP	Certificate of Suitability of the Ph.Eur.
CHMP	Committee for medicinal products for human use
C_{max}	Maximum measured plasma concentration
CoA	Certificate of Analysis
CAPA	corrective action-preventive action
CRS	Chemical Reference Substance (official standard)
CTAB	Cetyltrimethylammonium bromide
CV	Coefficient of variation
DCP	Decentralised Procedure
DD	Delivered Dose
DSC	Differential Scanning Calorimetry
EC	Ethics committee
EDQM	European Directorate for the Quality of Medicines
EMEA	European medicines agency
ERA	Environmental risk assessment
ET	Endothelin
EU	European union
GC	gas chromatography
GCP	Good clinical practise
GLM	General linear model
GLP	Good laboratory practise
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
HQC	High quality control
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INN	International nonproprietary name
INTQC	Intermediate quality control standard
IPC	In-process control test
IR	Infrared
ISR	Incurred sample reanalysis
ISTD	Internal standard
K_2EDTA	Dipotassium ethylene diamine tetra acetate
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LOD	(1) Limit of Detection, (2) Loss on Drying
LOQ	(1) Limit of Quantification, (2) List of Questions

MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
MV	Method validation
ND	Not detected
NDSRI	Nitrosamine Drug Substance-Related Impurities
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OECD	Organization for economic cooperation and development
PAH	Pulmonary arterial hypertension
PBT	Persistent, bioaccumulative and toxic (substance classification)
PDE	Permitted Daily Exposure
PE	Polyethylene
PEC	Predicted environmental concentration
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PP	Polypropylene
QC	Quality control
QOS	Quality Overall Summary
RH	Relative Humidity
RP	Restricted Part of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SAS	Statistical analysis system
SD	Standard deviation
SOP	Standard operating procedure
$T_{1/2}$	Terminal half-life
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
T_{max}	Time of the maximum measured plasma concentration
TYMC	Total Combined Yeast/Mould Count
UV	Ultraviolet
WHO	World health organisation
XR(P)D	X-Ray (powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare submitted on 26 April 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Macitentan Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'generic of a centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 February 2024.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Macitentan Accord as monotherapy or in combination, except in combination with phosphodiesterase-5 inhibitors, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Opsumit instead of non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Opsumit, 10 mg, film coated tablet
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 20-12-2013
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/13/893/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Opsumit, 10 mg, film coated tablet

- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 20-12-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/13/893/001-002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Opsumit, 10 mg, film coated tablet
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 20-12-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/13/893/002
- Bioavailability study number(s): 0159-23

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Nadrah

The application was received by the EMA on	29 April 2024
The procedure started on	23 May 2024

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 August 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 August 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 February 2025
The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality assessment of the product:	
– A GMP inspection at FP manufacturing site between 10-15 March 2025. The outcome of the inspection carried out was issued on	17 July 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	31 March 2025
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	25 April 2025
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	24 June 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 July 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Macitentan Accord on	24 July 2025
The CHMP adopted a report on similarity of Macitentan Accord with Winrevair on (Appendix on similarity)	25 April 2025

2. Scientific discussion

2.1. Introduction

The application for marketing authorisation of Macitentan Accord10 mg film-coated tablets is submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended. Essential similarity is claimed to the reference product Opsumit 10 mg film-coated tablets marketed by Janssen-Cilag International NV, authorised in the EU on 20th December 2013 (marketing authorisation numbers EU/1/13/893/001-002) via the centralised procedure (EMEA/H/C/002697).

To support this application, the applicant submitted one bioequivalence study in accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1). Also, ICH guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019) is relevant for the assessment.

The applicant indicated that Janssen-Cilag has been granted patent exclusivity for the following indications:

- until 28 August 2027: Macitentan in combination with PDE5-inhibitors for the treatment of pulmonary arterial hypertension (PAH).

- until 12 August 2029: Macitentan in combination with prostacyclin receptor (IP) agonists for the treatment of PAH.

The applicant requested to carve out the Macitentan in combination with PDE5-inhibitors and IP agonists for the treatment of PAH indication from the SmPC and sought marketing authorisation for the other approved indications including Macitentan as monotherapy.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 10 mg of macitentan as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, poloxamer 188, povidone k-30, magnesium stearate.

Film coating: polyvinyl alcohol (E1203), titanium dioxide (E171), talc (E553b), lecithin [soya] (E322), xanthan gum (E415).

The product is available in clear PVC/PE/PVDC blister pack or clear PVC/PVDC blister pack, as described in section 6.5 of the SmPC

2.2.2. Active substance

2.2.2.1. General information

The chemical names of macitentan are: {[5-(4-bromophenyl)-6-{2-[(5-bromopyrimidin-2-yl) oxy]ethoxy} pyrimidin-4-yl]sulfamoyl}(propyl)amine or N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl) oxy] ethoxy]-4-pyrimidinyl]-N'-propylsulfamide or Propylsulfamic acid N-[5-(4-bromophenyl)-6-[2-[(5-bromopyrimidin-2-yl)oxy]ethoxy]pyrimidin-4-yl]amide Sulfamide corresponding to the molecular formula $C_{19}H_{20}Br_2N_6O_4S$. It has a molecular mass of 588.24 g/mol and the following structure:

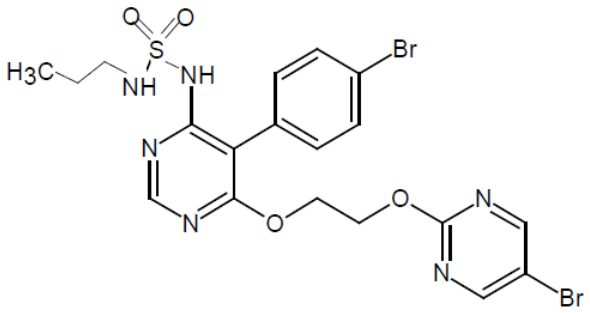

Figure 1: Active substance structure

The chemical structure of macitentan was elucidated by a combination of IR spectroscopy, proton and carbon NMR spectroscopy, mass spectroscopy, ultra-violet spectroscopy and elemental analysis. The solid-state properties of the active substance were measured by XRPD.

Macitentan is a white to off-white non-hygroscopic powder. It is freely soluble in dichloromethane and N,N-dimethyl formamide, soluble in acetone, very slightly soluble in methanol and practically insoluble in ethanol and water and aqueous buffers with pH from 1.2 to pH 7.6.

There is no monograph of macitentan active substance in European Pharmacopeia.

Macitentan has a non - chiral molecular structure, hence does not exhibit isomerism.

The active substance (AS) exhibits polymorphism. The active substance manufacturer consistently produces the same crystalline form of the active substance and XRPD is included in active substance specification.

2.2.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF.

Macitentan is synthesised in three chemical transformation steps followed by purification / crystallisation. Three starting materials were proposed initially for the synthesis. A major objection (MO) was raised requesting to define a fourth starting material as well. The applicant in their response defined the fourth starting material and provided detailed information regarding its control; the MO has been resolved. All starting materials are acceptable.

The manufacturing process is sufficiently described. Critical process parameters have been identified and limits for in process controls are stated. No recovery of materials and reprocessing is described in dossier.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. ICH M7 Classification for all possible impurities pertaining to active substance manufacturing process (starting from the starting materials) evaluated as per Derek Nexus and Sarah Nexus software has been included in section S.3.2. Risk assessment regarding potential presence of nitrosamines is provided. The results of a formal risk-assessment for the potential formation of nitrosamines, including all input materials, process intermediates and environmental factors of the process are provided. In the starting materials synthesis substances, which can lead to formation of nitrosamine impurities (NDEA and NDMA) are used. Confirmatory testing on 4 active substance batches shows that presence of NDEA and NDMA are below 10% of acceptable limit. Therefore, no control of NDEA and NDMA impurities are needed. A major objection (MO) was raised regarding potential formation of NDSRIs. The MO has been resolved, as it has been proven that formation of NDSRI is not possible.

The active substance is packaged in LDPE bag nitrogen gas purged and heat sealed which complies with EC 10/2011 as amended. This bag is placed in HMHDPE bag having silica gel sachets as desiccant, under nitrogen gas purged and heat-sealed. The outermost container closure is triple laminated aluminium bag and then placed in HDPE drum.

2.2.2.3. Specification(s)

The active substance specification includes tests for: appearance, solubility (Ph. Eur.), identification (IR, HPLC), polymorphism (XRD), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (HPLC), related substances (HPLC) and residual solvents (GC).

The specification for macitentan active substance applied by the finished product manufacturer is generally in line with specification followed by the ASMF holder. Additional test for particle size is included in specification. The proposed specification is acceptable. The maximum daily dose is 10 mg of macitentan and the corresponding specifications limits for impurities are in line with ICH guideline.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of 3 production size batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from three production size batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25ºC/60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested during stability studies*:* appearance, loss on drying, assay, related substances and polymorphism. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications. No trends of impurities or significant changes were observed. Stability of polymorphic form has been demonstrated.

Stability results from samples exposed on the following stress conditions: acid conditions (hydrochloric acid), base conditions (sodium hydroxide), oxidation (hydrogen peroxide), humidity (exposure to 75% relative humidity) and solid-state degradation (thermal and photo degradation) were also provided on

one batch. The results show that active substance degrades in alkali, acidic and oxidative condition and found to be stable in photolytic, thermal and humidity.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months stored in well-closed container under 25 °C.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product (FP) is a film-coated tablet (tablet) containing 10 mg macitentan. The tablets appear white to off-white, round, biconvex and are debossed with 'NL' on one side and plain on the other. There are no overages in the formulation.

The finished product has been developed to be a generic equivalent to the reference medicinal product Opsumit. Consequently, the objective was to prepare a film-coated tablet being essentially similar to the reference medicinal product.

The Quality target product profile and the critical quality attributes for macitentan film-coated tablets have been defined.

Formulation development trials to establish final composition of film-coated tablets were performed.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Excipient-active substance compatibility studies have been performed and showed that macitentan is compatible with studied excipients.

The qualitative composition of the FP is similar to the reference product Opsumit.

Stability of polymorphic form of active substance after 6 months at accelerated conditions has been demonstrated. The manufacturing process of macitentan tablets includes wet granulation step, therefore no additional data regarding stability of polymorphic form and particle size distribution of the active substance is requested.

The manufacturing process development has been described and is a typical wet granulation process. Critical quality attributes at in process and finished product stage were evaluated during scale up and relevant data was presented. Since the process includes a wet granulation step, no additional data regarding stability of polymorphic form and particle size distribution of AS was presented; this is acceptable. Studies were conducted to support the hold time for intermediate and bulk product. From the presented data there are no differences in the manufacturing process of the commercial product and clinical trial material.

A bioequivalence study with the reference product Opsumit 10 mg film-coated tablets has been performed and bioequivalence was demonstrated. Dissolution studies complementary to bioequivalence studies have been performed in different dissolution media. Based on F2 value results the dissolution profiles are similar in all tested media.

The development of the proposed dissolution method was presented. The method has been chosen based on AS solubility data and literature (US FDA's dissolution methods database). The AS is water insoluble so sink condition is possible only in the presence of surfactant. Solubility results reveal that

with lower amount of surfactant sink conditions are not achieved. A MO with regards to the paddle speed of 75 rpm for dissolution method was raised during the procedure. The applicant in their response further justified the paddle speed of 75 rpm showing that at lower speed the dissolution of the AS from the tablet was incomplete. The justification for the chosen dissolution method was accepted and thus the MO was resolved.

The discriminatory power of the proposed method has been demonstrated towards minor changes in formulation and towards changes in critical process parameters.

The primary packaging is clear PVC/PE/PVDC blister pack or clear PVC/PVDC blister pack. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

A MO was raised during the procedure in view of a Warning Letter issued by FDA concluding on GMP violations. The CHMP requested implementation of CAPAs and a reinspection to assess the implementation of CAPAs. Following the inspection performed by EU inspectors the CAPAs implementation was found satisfactory and a GMP certificate for the manufacturing site has been issued. Other sites involved in testing, batch release, and packaging have been clearly stated and sufficient evidence of GMP compliance has been presented for them.

The manufacturing process consists of four main steps: sifting, wet granulation, compression and film coating. The process is considered to be a standard manufacturing process.

The description of manufacturing process is provided in sufficient detail. Holding times for intermediate products are acceptable. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.2.3.3. Product specification(s)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), average tablet weight (gravimetric), identification (HPLC, UV), loss on drying (in house), dissolution (in-house), related substances (HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC) and microbial tests (Ph. Eur.).

The proposed set of specifications including analytical methods and respective limits is acceptable. The limits for specified impurities and unspecified impurities are in accordance with the ICH Q3B guideline. During the procedure a MO was raised regarding the suitability of the proposed dissolution specification limit requesting that it should be set based on results for the test biobatch. In response, the specification limit has been tightened in accordance with the dissolution results for the biobatch, and the MO is considered resolved.

A risk assessment on elemental impurities was provided. All potential risks according to ICH Q3D have been considered. Three process validation batches of commercial batch size have been tested for elemental impurities. Results for all elements are below 30 % of PDI according to ICH Q3D guideline. No control of elemental impurities in the finished product specification is needed.

A risk assessment on nitrosamine impurities has been presented in the initial submission. The CHMP considered the information insufficient and raised a MO requesting the applicant to consider the potential formation of AS-like nitrosamines in their risk assessment.
In the responses to day 120 LoQ potential formation of AS like nitrosamines has been considered. The updated risk assessment is in accordance with CHMP assessment report EMA/369136/2020 and was deemed satisfactory. All potential root causes identified in the Q & A document EMA/409815/2020 have been considered. Based on provided justification and negative results on AS the potential presence of AS like nitrosamine impurity can be excluded; the MO objection was thus resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification, dissolution, related substances, uniformity of dosage units and assay testing has been presented.

Batch analysis results are provided for three commercial batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, loss on drying, dissolution, related substances and microbiological quality. The analytical methods used were the same as for release and were stability indicating. All long term and accelerated stability results are within the proposed limits. There is a small trend observed for impurity I however well below specification limit.

Bulk stability data up to 12 months at long term conditions are provided. All results are within the proposed specification limits. The proposed 12 months shelf-life for bulk product is acceptable.

Photostability study on one batch of finished product has been performed in accordance with ICH guideline. All results are within specification limit. Film-coated tablets are photostable.

Based on available stability data, the proposed shelf-life of two years without special storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

2.2.3.5. Adventitious agents

None of the excipients used in this formulation are of human origin.

Lactose is of animal origin. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure a MO was raised related to the GMP

status of the proposed FP manufacturer, which was resolved after a re-inspection of the site to confirm implementation of appropriate CAPAs and issuing of a GMP certificate. Two MOs were raise*d* concerning the nitrosamine impurities risk assessment, and one MO was raised regarding the development of the dissolution method and the specification limit. The MOs were resolved by provision of additional data and tightening the dissolution specification limit as requested. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

The present application for Macitentan tablets 10 mg concerns a generic version of an already approved product, i.e. Opsumit 10 mg film-coated tablets manufactured by Janssen-Cilag International NV, Belgium. This product will be available as generic product and marketing authorization of the proposed product will most likely not lead to any increased environmental risk.

In Phase I of ERA, the applicant has calculated that the PECsw value with default Fpen (0.05 µg/L) was higher than the threshold for Phase II assessment. However, the PECsw refined by consumption and epidemiological data was below the 0.01 µg/L action limit, thus the phase II assessment was not required (see the Table below).

Partition coefficient octanol/water LogDow at pH 7.4 was 2.13, which indicates that Macitentan has low potential for bioaccumulation (FASS, Opsumit, 2024).

With no triggers for Phase II, the environmental risk assessment was concluded in Phase I. Additionally, the applicant's product is intended for a substitution of an approved product, therefore, this will not lead to an increased exposure to the environment.

Table 1. Summary of main study results

Substance (INN/Invented Name): macitentan			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	LogDow (pH 7.4) =2.13	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	LogDow (pH 7.4) =2.13	not B
	BCF	Unknown	B/not B
Persistence	DT50 or ready biodegradability	Unknown	P/not P
Toxicity	NOEC or CMR	Unknown	T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	Default= 0.05 Consumption= **0.004 µg/L** Epidimiological prevalence= 0.00075 µg/L	µg/L	> 0.01 threshold (N) Most relevant seems consumption data refined PECsw estimate
Other concerns (e.g. chemical class)	No.	N/A	(N)

2.3.3. Discussion on non-clinical aspects

This MAA is made on the basis that Macitentan tablets 10 mg is essentially similar to Opsumit 10 mg film-coated tablets manufactured/marketed by Janssen-Cilag International NV, Belgium. The indication sought for Macitentan tablets 10 mg are the same as those for Opsumit 10 mg film-coated tablets as monotherapy and carve out the Macitentan in combination with PDE5-inhibitors and IP agonists for the treatment of PAH indication from the SmPC. As this is a generic application claiming essential similarity to a currently marketed product, no non-clinical studies have been undertaken to support the application. Non-clinical overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by citing literature, collected by search engines of Pubmed and Science Direct. Literature search in regulatory databases and manual searches through the cross references of the studies were also performed to identify appropriate literatures/studies missed by the search strategy.

No additional impurities were observed in the test product, and the impurities profile can be considered to be essentially similar to the reference product. Additional information regarding nitrosamines and impurity limits has been added to Module 3.

The excipients used in the formulation of Macitentan tablets are the following: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone K 30, poloxamer 188, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, lecithin, xanthan gum.

All the excipients in the product are commonly used in solid oral dosage forms. It can be concluded that these excipients do not pose any significant safety or efficacy hazard under the conditions of use of the product.

The non-clinical sections of the SmPC are in line with the originator's SmPC and are acceptable.

A literature-based Phase I ERA has been provided by the applicant, which indicated that granting this MA will not pose any additional risk to the environment.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Macitentan Accord film-coated tablets from a non-clinical point of view.

2.4. Clinical aspects

Introduction

This application concerns a generic version of macitentan 10 mg film-coated tablets under trade name Macitentan Accord film-coated tablets.

The chosen reference medicinal product with recognised efficacy and an acceptable level of safety is Opsumit, which contains 10 mg of macitentan as film-coated tablets of Janssen-Cilag International NV, and authorised in the community on 20th December 2013 (marketing authorisation numbers EU/1/13/893/001-002) via the centralised procedure (EMEA/H/C/002697).

Both the test and reference product contain the same form of active substance - macitentan.

As this is an abridged application, the applicant has not conducted any efficacy or safety clinical studies with their formulation in support of this application. Macitentan is a well-known active substance with established efficacy and safety.

The present application is based on a literature overview with regard to the established efficacy and safety of macitentan and the bioequivalence study with Macitentan Accord 10 mg film-coated tablets compared to the originator product Opsumit 10 mg film-coated tablets.

The clinical overview on the clinical pharmacology, efficacy and safety is based on up-to-date and adequate scientific literature. Sufficient information on pharmacodynamic, pharmacokinetic and interactions of macitentan with other medicinal products are given. The Clinical overview addresses the proposed therapeutic indication, provided references support efficacy and safety of macitentan for proposed indication.

At the submission of application for marketing authorisation the indication in the proposed SmPC (section 4.1) was not entirely the same as indication in the SmPC of reference product Opsumit. In the proposed SmPC macitentan was not indicated in combination with phosphodiesterase-5 inhibitors while for reference product this restriction is not applied. Furthermore, in section 4.5 of proposed SmPC information on not clinically relevant interaction with sildenafil was missing in comparison with SmPC of reference product. In section 5.1 of proposed SmPC information on specific therapy for PAH at baseline in SERAPHIN study was missing in comparison with SmPC of reference product.

This is a generic application (Article 10(1) of Directive 2001/83/EC) where the intended use of generic medicinal product is a replacement of the reference medicinal product within the respective approved indications. The approved indications for macitentan are two separate entities: as monotherapy and combination therapy. Both entities were analysed separately at the time of the MA in the SERAPHIN trial (EPAR Table O-E-03): 739 patients were included, 268 received monotherapy (36,3%), 471 (63,7%) combination therapy. However, the combination therapy was almost exclusively based on patients receiving add-on treatment to PDE 5 inhibitors: Sildenafil (n= 426), Tadalafil (n=7) and Vardenafil (n=21). Only n=41 patients received other PAH specific medicinal products (Iloprost, Beraprost, Treprostinil, less than 10% of patients within the combination therapy group). For this reason it is questionable whether the proposed truncated combination indication is adequately supported by the data from the SERAPHIN trial, as the proposed indication disregards data on PDE-5 inhibitors, which accounted for 96% of the data supporting the combination indication in SERAPHIN. Moreover, excluding the combination of macitentan with PDE-5 inhibitors from the indication contradicts current clinical recommendations for the treatment of pulmonary arterial hypertension and may lead to confusion, Thus, the proposed indication was not acceptable. The applicant was advised to consider an indication where macitentan is used solely as monotherapy as it is sufficiently supported by the SERAPHIN trial (approximately one third of the total study population).

Indication was amended as suggested and also updated in line with the latest version of SmPC of reference product Opsumit: "Adults: Macitentan Accord as monotherapy 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). Paediatric population: Macitentan Accord as monotherapy 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)."

Information directly related to the combination therapy can be deleted from sections 4.1. therapeutic indications of the SmPC. For public health reasons, safety related information in sections 4.3 to 4.8. of the SPC should be maintained.

Information on interaction with sildenafil was included in section 4.5 of proposed SmPC as requested and information on study SERAPHIN in section 5.1 was aligned with reference SmPC. Subsection Paediatric population (aged ≥ 1 month to less than 2 years) in section 5.1 of proposed SmPC has been aligned with the latest version of SmPC of reference product Opsumit.

GCP aspect

The Clinical trial was performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

To support the application, the applicant has submitted one bioequivalence study (study No. 0159-23).

Tabular overview of bioequivalence study comparing Macitentan 10 mg film-coated tablets of Accord Healthcare S.L.U., to the already marketed reference product Opsumit 10 mg film-coated tablets of Janssen-Cilag International NV:

Table 2 Tabular overview of clinical studies

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
BE	0159-23	• m5-3-1-2-0159-23	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of macitentan tablets 10 mg in normal, healthy, adult human male subjects under fasting condition.	Two-period, two-sequence, single oral dose, crossover bioequivalence study under fasting condition	Macitenan tablets 10 mg, single dose, oral	42	Healthy, adult human male subjects	Single dose	Complete; Full

2.4.1. Clinical pharmacology

Pharmacokinetics

***Study* 0159-23**

One randomized, two-period, two-sequence, single dose crossover bioequivalence study under fasting condition to support this application is considered sufficient for an immediate release formulation, which can be taken with or without food. The selection of bioequivalence study is in accordance Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98).

Study No. 0159-23: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Macitentan Tablets 10 mg with Opsumit (Macitentan) 10 mg film-coated tablets of Janssen-Cilag International NV Turnhoutseweg 30 B-2340 Beerse Belgium in normal, healthy, adult, human male subjects under fasting condition

Protocol No. 0159-23, version 1.0 (dated 24th April 2023)

Table 3 Summary of study information:

Clinical Facility and Quality Assurance Services:	Lambda Therapeutic Research Limited, Shiv Ganga 2, Opposite D-Mart, Panchot Circle, Mehsana-384002, Gujarat, India.
Pharmacokinetic, Bio-analytical, Bio-statistics and Programming, Quality Assurance and Clinical Laboratory Services:	Lambda Therapeutic Research Ltd., Lambda House, Plot No. 38, Survey no. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-382481, Gujarat, India.
Sponsor:	Intas Pharmaceuticals Limited, India
Principal investigator:	Dr. Nikit Patel, M.B.B.S.
Study Period:	Study initiation date: 21st December 2023 Study completion date: 4th January 2024
Bioanalytical Phase Dates:	Experimental start date: 1st January 2024 Experimental completion date: 13th January 2024

Date of the Clinical Study Report:	27th February 2024 (version 00)

Methods

Study design

This study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study in normal, healthy, adult human subjects under fasting condition. The study was conducted under fasting conditions, which is acceptable as the drug product can be taken with or without food and the fasting condition is the most sensitive to identify differences between the formulations.

After an overnight fast of at least 10 hours, a single oral dose (10 mg) of either the test product or the reference product was administered to the subjects with 240 ± 02 mL of drinking water at ambient temperature in sitting posture in each period. The IMP administration was as per the randomization schedule and under open label conditions.

Dosing dates were 22nd December 2023 (Period I) and 31st December 2023 (Period II).

A washout period of 9 days was maintained between the successive dosing days. The washout period of 9 days is long enough in regard to the half-life of the studied active substance macitentan. It is longer than 5 times half-life of active substance (5 x 16 hours).

Subjects were checked-in clinical site at least 11 hours before drug administration and checked-out 48 hours after drug administration in both study period.

Parent compound (macitentan) was analysed in plasma samples.

The venous blood samples were withdrawn at pre-dose (0.000 hour) and at 1.000, 2.000, 3.000, 4.000, 4.500, 5.000, 5.500, 6.000, 6.500, 7.000, 7.500, 8.000, 8.500, 9.000, 9.500, 10.000, 10.500, 11.000, 12.000, 16.000, 24.000, 36.000, 48.000, 72.000 and 96.000 hours post dose in each period. Blood sample at and after 72.000 hours post-dose was collected as ambulatory sample. The sampling scheme to estimate pharmacokinetic parameters for conclusion regarding bioequivalence is adequate (frequent sampling around predicted T_{max} (according to reference SmPC T_{max} of macitentan is about 8 hours), at least 3-4 samples during the terminal log-linear phase for individual subject). Sampling period (96 hours) is long enough for concerned immediate-release drug product (apparent elimination half-life of macitentan is approximately 16 hours). Furthermore, according to the Guideline on the investigation of bioequivalence a sampling period longer than 72 h is not considered necessary for any immediate release formulation irrespective of the half-life of the drug.

Fluid intake was standardized. Posture and physical activities after dosing were standardized. There were some restrictions (regarding taking some food and drinks, alcohol, tobacco, recreational drugs, unusual diet, concomitant medication) that subjects were to comply with prior to and during the course of this study.

Meals taken after dosing were standardised in regard to composition and time of administration during an adequate period of time and was the same in both periods.

Test and reference products

Detailed information on the proposed and reference product used in bioequivalence study 0159-23 are provided. in the following table:

Table 4 Test and reference products

Product Characteristics	Test Product	Reference Product
Name	Macitentan Tablets 10 mg	Opsumit® 10 mg film coated tablets
Strength	10 mg	10 mg
Dosage form	Tablet	Tablet
Manufactured by	Intas Pharmaceuticals Ltd., India.	Janssen Pharmaceutica NV Turnhoutseweg 30 B-2340 Beerse Belgium.
Marketing Authorization Holder	-	Janssen-Cilag International NV Turnhoutseweg 30 B-2340 Beerse Belgium.
Batch / Lot number	M2311243	ZE035B0601
Batch size (Biobatch)	220000 tablets	
Measured content(s) (% of label claim)	99.1%	98.5%
Commercial Batch Size	-	-
Expiry date (Retest date)	July 2025	December 2026
Location of Certificate of Analysis	Module 5, Section 5.3.1.2, study-intro	Module 5, Section 5.3.1.2, study-intro
Member State where the reference product is purchased from:		Romania
This product was used in the following trials	0159-23	0159-23

The Certificates of analysis for the test and reference product bio-batch are provided. The assayed content of the batch used as test product does not differ more than 5% from that of the batch used as reference product.

The batch size of the test biobatch (220.000 tablets) is equivalent to the production batch size and thus appropriate.

The reference product is registered in EU and obtained from the EU Member State Romania, which is acceptable.

In Module 3 it is confirmed that the test product used in the bioequivalence study has the same qualitative and quantitative composition and is manufactured by the same manufacturing process as the medicinal product submitted for authorisation.

Comparative dissolution profiles of first three production size batches in QC medium (bio-batch vs 2 other production (validation) batches) were provided and are similar.

Population(s) studied

The population chosen is according to the Guideline on the investigation of bioequivalence. Only male subjects participated in the study, they met all the inclusion criteria and none of the exclusion criteria described in the study protocol.

A total of 45 subjects were checked in for Period-I of the study. 3 subjects were checked in for the study, in order to compensate for any dropout prior to dosing in Period-I. All the extra subjects were

checked out of the facility as none of the subjects discontinued/were withdrawn from the study prior to dosing in Period-I. Hence, a total of 42 subjects were dosed in Period-I of the study.

Two subjects were discontinued from the study on their own accord in Period-II, one subject was withdrawn from the study on medical grounds in Period-II and one subject discontinued from the study on his own accord in Period-II. Further, he was withdrawn from the study on medical grounds in Period-II.

38 subjects completed the clinical phase of the study successfully and were included in pharmacokinetic and statistical analysis.

Plasma samples of all 42 subjects were analysed. In which, withdrawn subjects were also analysed as per protocol requirement. Sample concentration for discontinued subjects are presented.

The demographic data are presented and are appropriate.

Sample size calculation is presented and is appropriate. Sample size is adequate.

In Clinical study report only sampling deviations and missing samples were reported as protocol deviations. Since the actual times were used for computation in pharmacokinetic and statistical analysis, the sampling time deviations are not expected to have any impact on the overall assessment of the study. List of sampling time point deviations used for pharmacokinetic evaluation has been presented. Missing samples were only 2 (subjects 1026 and 1039 did not report for 72.000 hours ambulatory sample collection in Period-I) and were disregarded in pharmacokinetic and statistical analysis, therefore it is considered to have no impact on the overall assessment of the study.

Analytical methods

Pre-study method validation

The bioanalytical LC-MS/MS method for the quantification of macitentan in human plasma (containing K_2EDTA as an anticoagulant) was validated according to in-house SOP on Bioanalytical Method Validation.

Main bioanalytical method validation has been performed between 4th September and 20th September 2019, and validation report dated 25th October 2019 has been enclosed. Later, partial validations have been performed: Addendum II (June/July 2021) and Addendum III (October/November 2022).

Bioanalytical method validation was performed at the bioanalytical facility.

Validation report for main bioanalytical method validation, Addendum II and Addendum III have been enclosed. Validation plan, method SOP and bioanalytical method validation SOPs have been enclosed.

Quality assurance statement and investigator's (or director's) declaration on GLP compliance have been included in main validation report and in both Addendums. Certificates of analysis of reference standards and internal standards used in main validation and both Addendums have been enclosed.

During main method validation one deviation from validation plan has been observed (sensitivity experiment performed without authorization). It is considered having no impact for overall outcome of the data. There has been no observed deviation in both Addendums.

The following parameters requested according to ICH guideline M10 on bioanalytical method validation and study sample analysis have been successfully validated after change in instrument and change in rinsing solution (Addendum III, the same instrument and rinsing solution as for study sample analysis): selectivity, specificity in the presence of concomitant drugs (hyoscine butyl, pheniramine, pantoprazole), calibration range and linearity, precision and accuracy, dilution integrity, sensitivity, auto sampler carry over, stability (short term solution stability of macitentan and ISTD, long term solution

stability of macitentan). Other requested stabilities (short term stock solution stability of drug, short term spiking solution stability of drug at higher level, short term spiking solution stability of drug at lower level, short term stock solution stability of ISTD, short term intermediate ISTD dilution stability, long term stock solution stability of drug, long term spiking solution stability of drug at higher level, long term spiking solution stability of drug at lower level, long term stock solution stability of ISTD, long term intermediate ISTD dilution stability, whole blood stability, auto sampler /wet extract stability, freeze and thaw stability, bench top stability, wet extract bench top stability, long term stability in human plasma), selectivity in the presence of metabolite N-despropyl macitetan, recovery, matrix effect and reinjection reproducibility have been validated within main validation and Addendum II (applying different instrument and rinsing solution as for study sample analysis).

It was adequately justified that the specificity in the presence of metabolites, recovery, matrix effect and reinjection reproducibility was already validated during main method validation and same is applicable for updated method (after change in instrument, change in rinsing solution).

Table of all runs (including failed runs) with analysis dates, table of calibration standard concentration and response functions results (calibration curve parameters) of all accepted runs with accuracy and precision, representative chromatograms, 100% method validation chromatograms and 100% of run summary tables of accepted and failed runs have been enclosed.

Bioanalytical method validation is considered to ensure the acceptability of assay performance and the reliability of analytical results.

Analysis of study samples and within-study validation

Bioanalytical report Determination of macitentan concentrations in study samples collected during clinical study No. 0159-23, version 00, dated 27th February 2024 has been enclosed.

The bioanalytical phase of the study was conducted as per bioanalytical study plan Determination of macitentan concentrations in study samples collected during clinical study No. 0159-23, version 00, dated 23rd December 2023, which has been enclosed. Furthermore, all relevant bioanalytical SOPs have been enclosed.

The sample analysis was performed at the bioanalytical facility. Bioanalytical phase has been performed from 1st January to 13th January 2024.

First study sample was collected on 22nd December 2023 and last study sample was analysed on 13th January 2024. Maximal storage period of study samples was 23 days between -80.61°C and -56.85°C. Long-term stability of macitentan in K_2EDTA human plasma was established for 660 days at -22 ± 5°C and 659 days at -65 ± 10°C.

Table 5 Study samples details:

Number of subjects as per protocol	42
Number of study periods as per protocol	2
Number of sampling points per period as per protocol	26
Number of study samples as per protocol	2184 (42 x 2 x 26)
Number of samples received	2078
Missing samples	106 26 samples (period II subject 1003) 26 samples (period II subject 1020)

	26 samples (period II subject 1022) 26 samples (period II subject 1032) 1 sample (period I, 72h sample of subject 1026) 1 sample (period I, 72h sample of subject 1039)
Number of samples analysed	2078

The analytical method used for the study samples analysis is the same as the validated method. The plasma concentrations of Macitentan in the subject samples were determined by a validated LC-MS/MS method using Macitentan-d4 as an internal standard. The analyte and internal standard were extracted from plasma by solid phase extraction method extraction method. Details related to extraction method, chromatographic conditions, mass spectrometric conditions and integration parameters are described in Method SOP No. MS-1694-00. The concentrations of Macitentan in human plasma were measured using an 8-point calibration curve with concentrations ranging from 2.031 ng/mL to 399.136 ng/mL. The concentrations of the standards for subject samples were calculated using linear regression analysis with a weighting factor of $1/concentration^2$.

Analytical method has been suitably within-study validated. Subject samples were processed with calibration curve standards, blank and zero standards, interspersed quality control samples, blank samples and subject samples with all-time-points of particular period of each subject positioned as consecutive samples. All analytical runs (23) were accepted. There was no failed analytical run. There were no re-injections.
Accepted analytical runs met analytical run acceptance criteria. The range of precision and accuracy of the back-calculated concentrations of the calibration curve standard points during the study were 0.7% to 1.5% and 98.2% to 101.9% respectively. The inter-day precision and accuracy of quality control samples during the study were 2.7% to 4.6% and 101.2% to 104.0%. Carry-over has been tested with-in each analytical run (HQC samples followed with blank QC samples).

10 individual samples were reanalysed. Reason for reanalysis (no ISTD response obtained, significant variations in response of internal standard) is predefined in SOP on Repeat analysis and acceptance of results. Original, repeat and reported values are presented. Repeat values were reported, which is in line with SOP.

160 of 2078 study samples were considered for ISR evaluation. It represents more than 10% of the first 1000 study samples + 5% of the number of samples that exceed 1000 samples. Results of incurred sample reanalysis confirmed the reproducibility of the analytical method (100.0 % of the reanalyzed samples met the acceptance criteria of method reproducibility).

100% of run summary tables of analytical runs are presented. 100% of chromatograms of analytical runs (including all chromatograms of CC, QC, blank and zero samples) are presented. IS response plots for each analytical run are presented. There was no re-integration in this study. No manual integration of chromatographic peaks was performed.

According to Bioanalytical report (page 17/46) during clinical phase of the study, some of the concomitant medications were administered to subject 1006. However, according to Study report only subjects 1020 and 1022 received concomitant medications. Clarification was requested. The applicant has clarified, that it was a mistake in Bioanalytical report, section 9.0 Impact assessment of concomitant drugs. The correction has been made.

The method was sensitive enough to quantify levels of 5% of the lowest C_{max} measured in the study.

Quality assurance statement and study director's declaration on GLP compliance have been included in bioanalytical report. Certificates of analysis of reference standard and internal standard used in study sample analysis have been enclosed.

There were no SOP and no protocol deviations during subject sample analysis. There were no bioanalytical issues during subject sample analysis.

Pharmacokinetic variables

The following pharmacokinetic parameters were calculated:
Primary pharmacokinetic parameters: C_{max} and AUC_{0-t}
Secondary pharmacokinetic parameter: T_{max}, $AUC_{0-\infty}$, λ_z, T½ and AUC_%Extrap_obs

These pharmacokinetic parameters were calculated for macitentan using the non-compartmental model of Phoenix WinNonlin Version 8.3 (Certara L.P.).

Actual time-points of sample collection are used for the calculation of pharmacokinetic parameters.

All concentration values below the lower limit of quantification are set to zero for the pharmacokinetic and statistical calculations.

Statistical methods

Descriptive statistics were to be calculated and reported for the pharmacokinetic parameters for macitentan.

The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} were to be subjected to Analyses of Variance (ANOVA) for macitentan.

ANOVA model was to be include sequence, subject (sequence), period and formulation as fixed effects.

Each analysis of variance included calculation of least-squares means, the difference between the adjusted formulation means and the standard error associated with this difference.

An F-test was to be performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha = 0.05).

The power of the study was to be computed and reported for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for macitentan.

Ratio of geometric least squares means of test and reference product was to be computed and reported for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for macitentan.

Intra-subject variability was to be calculated and reported for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for macitentan.

Any missing samples or non-reportable concentration values were to be disregarded in pharmacokinetic and statistical analysis.

90% confidence intervals for the ratio of geometric least squares means between drug products were to be computed for ln-transformed data of C_{max} and AUC_{0-t} for macitentan.

All statistical analyses for macitentan were performed using PROC GLM of SAS Version 9.4 (SAS Institute Inc., USA).

Criteria for conclusion of bioequivalence were as follows:

Bioequivalence of Test Product-T vs. Reference Product-R is concluded, if the 90% confidence interval for the ratio of geometric least square means falls within the acceptance range (80.00 – 125.00%) for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for macitentan.

Results

The pharmacokinetic variables of macitentan for test and the reference product and statistical evaluation of macitentan pharmacokinetic variables are shown in the following tables:

Table 6: Pharmacokinetic parameters for macitentan (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ (ng.h/mL)	5318.164	1263.1666	5168.233	1299.1302
$AUC_{(0-\infty)}$ (ng.h/mL)	5422.327	1281.6904	5285.225	1347.5434
C_{max} (ng/mL)	203.613	42.0091	195.315	42.2003
T_{max}* (h)	7.500 (4.500 - 16.000)		7.500 (4.500 - 12.000)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 7: Statistical analysis for macitentan (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	103.1	99.98-106.30	7.9
C_{max}	104.5	99.66-109.56	12.3
* estimated from the Residual Mean Squares			

Bioequivalence has been shown appropriately.

The test to reference ratio of geometric least squares means with corresponding 90% CI for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} was within the acceptance range of 80.00-125.00% for macitentan. Therefore, the test product-T is considered to be bioequivalent to the reference product-R under fasting condition.

T_{max} values have been determined, which were comparable between test and reference products.

C_{max} of macitentan was not the first point of a concentration time curve in any subject.

Pre-dose plasma concentration of macitentan was below the limit of quantitation (2.031 ng/mL) for all subjects in both periods.

All subjects had macitentan plasma concentration curves where extrapolated area was <20%.

Following ANOVA evaluation of pharmacokinetic parameters statistically significant sequence effect was observed for AUC_{0-t}. The applicant has provided adequate clarification that this significant sequence effect is just statistically significant and can be ignored.

Safety data

There were no deaths or serious adverse events during the conduct of the study. In general, the clinical portion of the study was completed with 4 adverse events, out of which, 2 adverse events were significant. The investigational products were well tolerated by healthy subjects, as a single dose administration. The results from all subjects, who completed post-study procedures including

laboratory tests and vital signs measurements, confirmed the absence of significant changes in the subjects' state of health.

2 subjects who received concomitant medication due to adverse events were withdrawn from the study on medical grounds, therefore, concomitant medications do not have any impact on study results. Both subjects were treated appropriately and followed up until resolution of their adverse events.

Pharmacokinetic conclusion

Based on the presented bioequivalence study No. 0159-23 proposed product Macitentan Accord 10 mg film-coated tablets is considered bioequivalent with reference product Opsumit 10 mg film-coated tablets.

Additional data

The comparative in-vitro dissolution profile between test and reference product used in bio-equivalence study has been generated in pH 6.8 Phosphate buffer + 0.05% CTAB (Q.C. media), 0.1 N HCl 0.05% CTAB and pH 4.5 Acetate buffer 0.05% CTAB as per below details.

The condition for dissolution method is as follows:

Table 8 condition for dissolution

Dissolution Parameters	
Medium	pH 6.8 Phosphate buffer + 0.05% CTAB (Q.C. media) 0.1 N HCl + 0.05% CTAB pH 4.5 acetate buffer + 0.05% CTAB
RPM	75 RPM
Volume	900 ml
Apparatus	Apparatus Type 2 (Paddle)

Comparative dissolution profile between test and reference product used for bioequivalence studies:

Table 9 Comparative dissolution profile between test and reference product used for bioequivalence studies:

Formulation		Dissolution Medium	F_2 Value
Opsumit 10 mg film coated tablets (Batch No.: **ZE035B0601**) **(BE reference batch)**	Macitentan 10 mg film-coated tablets (Batch No.: **M2311243**) **(BE test batch)**	pH 6.8 Phosphate buffer + 0.05% CTAB (Q.C. media)	77.4
		0.1 N HCl + 0.05% CTAB	80.9
		pH 4.5 acetate buffer + 0.05% CTAB	54.6

Comparative dissolution profiles between biobatches of test and reference product (10 mg strength) are considered similar in all tested media (pH 6.8 Phosphate buffer + 0.05% CTAB (Q.C. media), 0.1 N HCl 0.05% CTAB and pH 4.5 Acetate buffer 0.05% CTAB) based on f2 calculation (f2 > 50), conditions for f2 calculation according to Guideline on the investigation of bioequivalence, Appendix I are fulfilled.

Experimental conditions for in vitro dissolution experiment are not in accordance with Guideline on the investigation of bioequivalence, Appendix III. Rotation speed of paddle apparatus is too high, surfactant is added in dissolution media. However, since bioequivalence of those products has been demonstrated in vivo, it prevails and no issue regarding dissolution method is raised.

Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2. Clinical efficacy

No new studies were submitted, and none are required for applications of this type. Efficacy of the present formulation is based on the efficacy of the previously approved reference product.

2.4.3. Clinical safety

No new studies were submitted, and none are required for applications of this type. Safety of the present formulation is based on the safety of the previously approved reference product.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5. Discussion on clinical aspects

To support the application, the applicant has submitted a review of clinical data as well as a randomised, two-period, two-sequence single dose crossover bioequivalence study under fasting conditions to demonstrate essential similarity with the reference product Opsumit film-coated tablets.

According to the SmPC of the reference product, macitentan can be taken with or without food. Therefore, the conduct of the single dose study under fasting condition to detect a potential difference between formulations is justified and in accordance with bioequivalence guidelines. The bioequivalence study was conducted under standardised conditions. The washout period of 9 days is long enough in regard to the half-life of the studied active substance macitentan. Sampling period was sufficient, sampling time schedule was adequate.

Data regarding the test and reference product are provided. The assayed content of the batch used as test product does not differ more than 5% from that of the batch used as reference product. The batch size of the test bio-batch (220.000 tablets) is equivalent to the production batch size. The reference product is registered in EU and obtained from the EU Member State Romania. In Module 3 it is confirmed that the test product used in the bioequivalence study has the same qualitative and quantitative composition and is manufactured by the same manufacturing process as the medicinal product submitted for authorisation. Comparative dissolution profiles of first three production size batches in QC medium (bio-batch vs 2 other production (validation) batches) were provided and are similar.

A total of 45 subjects were checked in for Period-I of the study. All the checked in subjects satisfied all the inclusion and exclusion criteria. 3 subjects of them were checked in for the study, in order to compensate for any dropout prior to dosing in Period-I. All the extra subjects were checked out of the facility as none of the subjects discontinued/were withdrawn from the study prior to dosing in Period-I. Hence, a total of 42 subjects were dosed in Period-I of the study. 2 subjects discontinued from the study on their own accord in Period-II, 1 subject was withdrawn from the study on medical grounds in Period-II and one subject initially was considered discontinued from the study on his own accord in Period-II. Further, he was withdrawn from the study on medical grounds. 38 subjects completed the clinical phase of the study successfully and were included in pharmacokinetic and statistical analysis. Plasma samples of all 42 subjects were analysed (withdrawn subjects were also analysed as per protocol requirement and concentration were presented). Case Report Forms for all discontinued subjects have been provided and confirm information on discontinuation.

The bioanalytical method (LC-MS/MS) for quantification of macitentan (parent drug) in human K_2EDTA plasma samples was pre-study and within study validated according to ICH guideline M10 on bioanalytical method validation and study sample analysis. Bioanalytical report and validation reports have been

enclosed. Bioanalytical method is considered acceptable for study samples analysis. Handling of samples was adequate.

Pharmacokinetic was primarily assessed by the pharmacokinetic properties of the test and reference formulations by measurement macitentan concentrations in plasma. The following pharmacokinetic parameters were calculated: C_{max} and AUC_{0-t} (primary pharmacokinetic parameters) and T_{max}, $AUC_{0-\infty}$, λ_z, T½ and AUC_%Extrap_obs (secondary pharmacokinetic parameters). The pharmacokinetic variables investigated in study to determine bioequivalence after a single dose are in line with the Guideline on the Investigation of Bioequivalence and are thus considered appropriate. Pharmacokinetic parameters for macitentan were calculated using non-compartmental methods. The software used for determination of pharmacokinetic parameters was Phoenix WinNonlin Version 8.3 (Certara L.P.). Actual time points of the sample collection were used for the calculation of pharmacokinetic parameters.

The statistical method used for the pharmacokinetic analyses is considered acceptable. Data transformations and statistical tests used are acceptable. The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} were subjected to analysis of variance (ANOVA) for macitentan. The ANOVA model included sequence, subject (sequence), period and formulation as fixed effects. All statistical analyses for macitentan were performed using the PROC GLM of SAS Version 9.4 (SAS Institute Inc., USA).

The criteria for bioequivalence were predefined and are acceptable. The test to reference ratio of geometric least squares means with corresponding 90% CI for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} was within the acceptance range of 80.00-125.00% for macitentan. Therefore, the test product-T is considered to be bioequivalent to the reference product-R under fasting condition.

There were no deaths or serious adverse events during the conduct of the study. The investigational products were well tolerated by healthy subjects, as a single dose administration. The results from all subjects, who completed post-study procedures including laboratory tests and vital signs measurements, confirmed the absence of significant changes in the subjects' state of health.

Appropriate statements on GCP have been provided. The applicant has provided a list of inspections of clinical site and bioanalytical site where bioequivalence study was conducted. The applicant has provided further information on the outcome of the most recent inspections performed by EU competent authorities for clinical study site and bioanalytical study, PK and statistical analysis site. Monitoring reports for the bioequivalence study No. 0159-23 have been provided. There are no other observations, which could have raised concerns about the quality or validity of the sampling process or study sample analyses, the analytical method validation or the statistical analysis.

Comparative dissolution profiles between biobatches of test and reference product (10 mg strength) are considered similar in all tested media (pH 6.8 Phosphate buffer + 0.05% CTAB (Q.C. media), 0.1 N HCl 0.05% CTAB and pH 4.5 Acetate buffer 0.05% CTAB) based on f2 calculation (f2 > 50).

The clinical overview on the clinical pharmacology, efficacy and safety of macitetan is adequate.

Indication in proposed SmPC was amended as suggested (the applicant was advised to consider an indication where macitentan is used solely as monotherapy as it is sufficiently supported by the SERAPHIN trial) and also updated in line with the latest version of SmPC of reference product Opsumit: "Adults: Macitentan Accord as monotherapy 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). Paediatric population: Macitentan Accord as monotherapy 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)."

Information on interaction with sildenafil was included in section 4.5 of proposed SmPC as requested (In line with the Q and A guidance (Question 2.9) Generic and hybrid applications | European Medicines Agency (EMA) (europa.eu) sections 4.3 to 4.8 should be aligned with the originator regarding safety information) and information on study SERAPHIN in section 5.1 was aligned with reference SmPC.

Overall, proposed SmPC was aligned with the latest version of reference SmPC, except indication in combination (section 4.1) and the sentence on the positive B/R of the combination with sildenafil in section 4.5 due to existence of pending patents protecting a therapeutic indication of the original marketing authorisation application in one or more Member States.

2.6. Conclusions on clinical aspects

Based on the presented bioequivalence study No. 0159-23 proposed product Macitentan Accord 10 mg film-coated tablets is considered bioequivalent with reference product Opsumit 10 mg film-coated tablets.

Efficacy and safety of the proposed product is based on the efficacy and safety of the previously approved reference product Opsumit. The clinical overview on the clinical pharmacology, efficacy and safety of macitentan is adequate. Proposed SmPC was aligned with the latest version of reference SmPC, except indication in combination (section 4.1) and the sentence on the positive B/R of the combination with sildenafil in section 4.5 due to existence of pending patents protecting a therapeutic indication of the original marketing authorisation application in one or more Member States.

2.7. Risk management plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

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

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Safety concerns (Important identified risks)	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	Routine risk minimisation measures: –SmPC sections 4.3, 4.4 and 4.8. –PL sections 2 and 4. -Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of liver injury (e.g. Jaundice), macitentan treatment should be discontinued, is included in SmPC section 4.4. –Reinitiation of macitentan may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury. The advice of a hepatologist is recommended, is included in SmPC section 4.4. • The prescription only status of the product. Additional risk minimisation measures: • Risk minimisation tools (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. –PL section 2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Macitentan Pregnancy and Outcome Follow-Up Questionnaire.

Safety concerns (Important identified risks)	Risk minimisation measures	Pharmacovigilance activities
	-Macitentan treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised, is included in SmPC sections 4.3 and 4.6. Women should not become pregnant for 1 month after discontinuation of macitentan. Monthly pregnancy tests during treatment with macitentan are recommended to allow the early detection of pregnancy, is included in SmPC section 4.4. • The prescription only status of theroduct. <u>Additional risk minimisation measures</u>: • Risk minimisation tools (Patient card).	<u>Additional pharmacovigilance activities</u>: None.

2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Irinotecan hydrochloride. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of macitentan film-coated tablets. The reference product Opsumit is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III as monotherapy or in combination and in paediatric patients aged less than 18 years and bodyweight ≥ 40 kg with WHO Functional Class (FC) II to III as monotherapy or in combination. No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

The bioequivalence study forms the pivotal basis with a randomized, single dose, 2-treatment, 2-period, 2-sequence, crossover design under fasting conditions. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Fasting conditions are appropriate since SmPC of reference product Opsumit recommends dosing 'with or without food' and fasting conditions are considered the most sensitive condition to detect potential differences between formulations. Concentration of parent drug macitentan were measured in plasma samples. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The test formulation of Macitentan Accord 10 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the reference product Opsumit 10 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%.

Bioequivalence of the two formulations is considered to be demonstrated.

Having considered the data submitted in the application and available on the chosen reference medicinal product, the following additional risk minimisation activities are necessary for the safe and effective use of the medicinal product:

• Patient Card

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The application contains **adequate quality data**.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP is by consensus of the opinion that macitentan Accord is not similar to Winrevair (Sotatercept) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Macitentan Accord is favourable in the following indication:

Adults

Macitentan Accord as monotherapy 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).

Paediatric population

Macitentan Accord as monotherapy 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).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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 European Medicines Agency;
- 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.

- **Additional risk minimisation measures**

- Patient Card