COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sacubitril/Valsartan WinMedica 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, film-coated tablets (sacubitril sodium & valsartan disodium)

NL/H/6007/001-003/DC

Date: 10 February 2026

This module reflects the scientific discussion for the approval of Sacubitril/Valsartan WinMedica 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets. The procedure was finalised on 18 June 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 Sacubitril/Valsartan WinMedica 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets, from Win Medica S.A.

The product is indicated for:
Adult heart failure
The product is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Paediatric heart failure
The product is indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction.

A comprehensive description of the up-to-date indications and posology is given in the 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 Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/15/1058).

The concerned member states (CMS) involved in this procedure were Cyprus and Germany.

II. QUALITY ASPECTS

II.1 Introduction

Sacubitril/Valsartan WinMedica 24 mg/26 mg is a violet white, round film-coated tablet, unscored, debossed with “L” on one side and plain on the other side. The approximate tablet diameter is 6.0 mm. Each 24 mg/26 mg film-coated tablet contains as active substances 24.3 mg sacubitril (as sacubitril sodium) and 25.7 mg valsartan (as valsartan disodium).

Sacubitril/Valsartan WinMedica 49 mg/51 mg is a pale yellow, ovaloid biconvex film-coated tablet, unscored, with bevelled edges, debossed with “I” on one side and plain on the other side. The approximate tablet dimensions are 13.1 mm x 5.2 mm. Each 49 mg/51 mg film-coated tablets contains as active substances contains 48.6 mg sacubitril (as sacubitril sodium) and 51.4 mg valsartan (as valsartan disodium).

Sacubitril/Valsartan WinMedica 97 mg/103 mg is a light pink, ovaloid biconvex film-coated tablet, unscored, with beveled edges debossed with "H" on one side and plain on the other side. The approximate tablets dimensions are 15.1 x 6.0 mm. Each 97 mg/103 mg film-coated tablets contain as active substances contains 97.2 mg sacubitril (as sacubitril sodium) and 102.8 mg valsartan (as valsartan disodium).

The excipients are:
Tablet core: cellulose microcrystalline (E460(i)), low-substituted hydroxypropylcellulose (E463), type A crospovidone, magnesium stearate and talc (E553b).
Film-coat: substitution type 2910 hypromellose (3 mPa·s), titanium dioxide (E171), talc (E553b), macrogol (4000), iron oxide red (E172), iron oxide black (E172)(24/mg 26 mg and 97 mg/103 mg only), iron oxide yellow (E172)(49 mg/51 mg only).

The 49 mg/51 mg and 97 mg/103 mg tablet strengths are dose proportional.

The film-coated tablets are packed in polyvinyl chloride/polychlorotrifluoroethylene (Aclar)//aluminum blisters (PVC/PCTFE (Aclar)//aluminum blisters), aluminum//aluminum & N2 blisters or aluminum//aluminum& desiccant blisters.

II.2 Drug Substance

Sacubitril sodium
One active substance is sacubitril sodium, an established active substance not described in the Pharmacopoeia. Sacubitril sodium is a crystalline powder and is freely soluble in water. For this product, polymorphic form 1 (manufacturer 1) and B (manufacturer 2) are consistently produced.

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
Manufacturer 1: The manufacturing process consists of a three step process with two intermediates. 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.

Manufacturer 2: The manufacturing process consists of six chemical transformation steps, followed by salification and purification, with three starting materials. 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 drug product manufacturer's in-house specifications. Additional specifications for particle size distribution (PSD) are set and justified. Microbiological activity is controlled through control of water activity. Stereoisomers of the active substance are controlled during production. Batch analytical data demonstrating compliance with this specification have been provided for three and six full-scaled batches (manufacturer 1 and 2 respectively).

Stability of drug substance

Stability data on the active substance have been provided for three and six production scaled batches (manufacturer 1 and 2 respectively) in accordance with applicable European guidelines demonstrating the stability of the active substance for 36 and 48 months (manufacturer 1 and 2 respectively) when stored under the stated conditions.

Valsartan disodium

The active substance is valsartan disodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Valsartan disodium is an amorphous powder that is also freely soluble in water. One polymorphic form is consistently produced.

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

Manufacturing process

Manufacturer 1: The manufacturing process consists of a five step process with one intermediate, followed by salification. Three starting materials are used. 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.

Manufacturer 2: The manufacturing process consists of a three step process with two intermediates, followed by hydrolysis and salification. 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 drug product manufacturer's in-house specifications. Additional specifications for PSD are set and justified. Microbiological activity is controlled through control of water activity. Batch analytical data demonstrating compliance with this

specification have been provided for five and three full-scale batches (manufacturer 1 and 2 respectively).

Stability of drug substance

Stability data on the active substance have been provided for three production scale batches per manufacturer in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 and 48 months (manufacturer 1 and 2 respectively) 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 choice of excipients is justified and their functions explained. Interchangeability of the active substances from different suppliers is sufficiently supported by development experience and physicochemical characteristics. The manufacturing process was based on the reference product and the high hygroscopicity of the active ingredients. Packaging was tested and selected based on the resistance to moisture ingress, which in stress studies was observed to lead to cracks in the tablets if not appropriately controlled. Dissolutions studies at 3 pHs (including QC) were adequately performed to support the bioequivalence studies and a biowaiver of strength for the three different strengths. Dissolution behaviour of the two active ingredients was shown to be comparable. A single QC dissolution method for both active substances with sufficient discriminatory power was established.

Manufacturing process

The manufacturing process consists of dry granulation, compression, coating and packaging. Due to the hygroscopic nature of the active substances, the manufacturing process is performed in a controlled low humidity environment. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three minimal size commercial batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements except for the colourants, which have specifications derived from the manufacturer. These specifications are acceptable.

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 weight, disintegration, uniformity of dosage units, identification of sacubitril, identification of valsartan, identification of colourants, water content, dissolution, assay, related substances and microbiological tests. The limits for average weight and water content are higher throughout the shelf life than at release, however, 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 three commercial scaled batches of each strength 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 scale batches of each strength stored at 25°C/60% RH (48 months) 30°C/75% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are "This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture."

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 Sacubitril/Valsartan WinMedica has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sacubitril/Valsartan WinMedica 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 Entresto 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

Sacubitril sodium and valsartan disodium are well-known active substances 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 Sacubitril and Valsartan 200 (97 +103) mg film-coated tablets (Win Medica S.A., Greece) was compared with the pharmacokinetic profile of the reference product ENTRESTO® (sacubitril and valsartan) 200 (97 +103) mg film-coated tablets (Novartis Europharm limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver
The MAH has submitted a biowaiver request for the lower strengths, i.e. Sacubitril/Valsartan 24 mg/26 mg and 49 mg/51 mg film-coated tablets. The following general requirements according to the EMA Bioequivalence guideline for the additional strengths are met:'

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all

strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Design

A open label, balanced, single-dose, randomised, four-period, two-treatment, two-sequence, crossover, full-replicate bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 22-45 years. Each subject received a single dose (97 and 103 mg) of one of the two sacubitril and valsartan formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period of 10 days.

Sacubitril

Blood samples were collected pre-dose and at 0.17, 0.25, 0.33, 0.42, 0.5, 0.67, 0.83, 1, 1.17, 1.33, 1.5, 1.67, 1.83, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 hours after administration of the products.

Valsartan

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.17, 1.33, 1.5, 1.67, 1.83, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Sacubitril/valsartan may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sacubitril/valsartan. 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

56 subjects were enrolled in the study. One subject was withdrawn in period I due to an adverse event (chest pain). Five subjects dropped out in period II, one due to an adverse event (fever), two due to non-compliance with study requirements, and two due to absence. One

subject dropped out of period IV due to an adverse event (high blood pressure). 51 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sacubitril, 97 mg under fasted conditions.

Treatment N= 99	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	2173.81 ± 558.107	2196.85 ± 558.860	2050.60 ± 850.286	0.50 (0.25 - 2.50)
Reference	2225.86 ± 510.924	2245.29 ± 511.148	2115.06 ± 890.424	0.50 (0.25 - 2.50)
***Ratio (90% CI) (N = 51)**	0.98 (0.95 – 1.00)	-	0.98 (0.91 – 1.06)	-

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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of valsartan, 103 mg under fasted conditions.

Treatment N= 99	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	31319.27 ± 11969.408	31639.77 ± 12154.698	4703.57 ± 1432.649	1.67 (1.00 - 4.00)
Reference	31091.22 ± 11866.253	31431.54 ± 12059.039	4587.39 ± 1368.602	1.67 (1.00 - 5.00)
***Ratio (90% CI) (N = 51)**	1.00 (0.94 - 1.07)	-	1.02 (0.96 - 1.09)	-

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

**ln-transformed values*

<u>Conclusion on bioequivalence study:</u>

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 Sacubitril/Valsartan WinMedica 97 mg/103 mg film-coated tablets is considered bioequivalent to Entresto 97 mg/103 mg film-coated tablets.

The results of study with 97 mg/103 mg formulation can be extrapolated to other strengths 24 mg/26 mg and 49 mg/51 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Sacubitril/Valsartan WinMedica. At the time of approval, the most recent version of the RMP was version 0.3 dated April 2025.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Embryo-fetal toxicity/lethality
Important potential risks	• Neonatal/infantile toxicity through exposure from breast milk • Cognitive impairment
Missing information	• Long term use of Sacubitril/Valsartan in HF patients

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 Entresto. 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

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

The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for

readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sacubitril/Valsartan WinMedica 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets has a proven chemical-pharmaceutical quality and are generic forms of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets. Entresto 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 Sacubitril/Valsartan WinMedica with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 June 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
-	-	-	-	-	-