COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sartesta 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets (sacubitril and valsartan)

NL/6035/001-003/DC

Date: 3 April 2026

This module reflects the scientific discussion for the approval of Sartesta 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets. The procedure was finalised on 20 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 Sartesta 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets, from Zaklady Farmaceutyczne Polpharma 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 state (CMS) involved in this procedure was Poland.

II. QUALITY ASPECTS

II.1 Introduction

Sartesta is a film-coated tablet.

Sacubitril/Valsartan 24 mg/26 mg is a white, biconvex, oval film-coated tablet debossed with "S7V" on one side and "L1" on the other side. Approximate tablet dimensions are 13 mm x 5 mm. Each film-coated tablet contains sacubitril sodium and valsartan disodium equivalent to 24.3 mg sacubitril and 25.7 mg valsartan.

Sacubitril/Valsartan 49 mg/51 mg is a pink, biconvex, oval film-coated tablet debossed with "S7V" on one side and "M2" on the other side. Approximate tablet dimensions are 12 mm x 5 mm. Each film-coated tablet contains sacubitril sodium and valsartan disodium equivalent to 48.6 mg sacubitril and 51.4 mg valsartan.

Sacubitril/Valsartan 97 mg/103 mg is a pink, biconvex, oval film-coated tablet debossed with "S7V" on one side and "H3" on the other side. Approximate tablet dimensions are 16 mm x 6

mm. Each film-coated tablet contains sacubitril sodium and valsartan disodium equivalent to 97.2 mg sacubitril and 102.8 mg valsartan.

The excipients are:
Tablet core: microcrystalline cellulose, low-substituted hydroxypropylcellulose, type A and type B crospovidone, talc, colloidal anhydrous silica, magnesium stearate.

Film coating: partially hydrolysed poly(vinyl alcohol), titanium dioxide, macrogol, talc, iron oxide red (E172) (49 mg/51 mg and 97 mg/103 mg only), iron oxide yellow (E172) (49 mg/51 mg and 97 mg/103 mg only).

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

The film-coated tablets are packed in oriented polyamide/aluminium/polyvinyl chloride-aluminium (oPA/Al/PVC-Al blisters).

II.2 Drug Substance

Sacubitril
The active substance is sacubitril sodium, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). It is an almost white to yellow powder and is freely soluble in water. It has two chiral centres and can exist in four isomers and is manufactured as the one form. The active substance shows polymorphism and the crystal form B is used.

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

Manufacturing process
The manufacturing process consists of three chemical transformation steps followed by a salification step. Two intermediates are isolated in the process. The process starts with one starting material. Ethanol and acetone are used in the last step. Two catalysts are used in the first step of the synthesis. No class 1 organic solvents are used in the process. 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 in-house requirements by the MAH and is largely in line with the specification of the ASMF with additional requirements for PSD and microbial quality. The tests for solubility was removed only one test for sodium identification is included instead of two included in the

specification of the ASM. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for six batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 48 months. Based on the data submitted, a retest period could be granted of 48 months when stored under the stated conditions.

Valsartan

The active substance is valsartan disodium, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder and is freely soluble in water. The active substance shows polymorphism and the crystal form 2 is used.

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

Manufacturing process

The manufacturing process consists of one manufacturing step. This step starts with an intermediate which has a Certificate of Suitability (CEP). No class 1 organic solvents are used in the process. 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 in-house by the MAH and is in general in line with the specification of the ASMF with additional requirements for particle size and polymorph form. Omission of microbial quality control is justified. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance

Stability data on the active substance have been provided for six batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 36

months. Based on the data submitted, a retest period could be granted of 36 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The main development studies performed were the characterisation of the reference products, establishment of a quality target product profile (QTPP) and deriving of critical quality attributes (CQAs) thereof, formulation optimisation studies and manufacturing process development. The development of the quality control (QC) dissolution method has been adequately justified and the discriminatory power of the method was shown. The choices of the packaging and manufacturing process are justified. Bioequivalence (BE) study was performed with the 24 mg/26 mg and 97 mg/103 mg strength versus the respective reference product strength. The test batches used in the BE study were manufactured according to the finalised composition and manufacturing process at a representative scale. For the additional 49 mg/51 mg strength a biowaiver is claimed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of mixing of the intra granular components followed by dry granulation, mixing with the extragranular components and lubrication, compression, film-coating and packaging. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for four production scale batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. requirements with additional control of functionality-related characteristics or in-house requirements (film-coating mixtures). 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, water content, uniformity of dosage units, identification, assay, dissolution and related substances. The release and shelf-life requirements/limits are identical for all parameters. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Adequate justification is provided for the absence of microbial control of the drug product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from four minimum commercial scaled batches per strength from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for four production batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable ICH 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 has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The post-approval commitment to perform manufacturing process validation for full-scale batches was made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sacubitril/Valsartan 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 and valsartan 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Sacubitril/Valsartan 24 mg/26 mg and 97 mg/103 mg film-coated tablets (Zaklady Farmaceutyczne Polpharma S.A., Poland) was compared with the pharmacokinetic profile of the reference product Entresto 26 mg/26 mg and 97 mg/103 mg film-coated tablets (Novartis, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study (pH 1.2, 4.5 and 6.8) results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

A biowaiver was requested for Sacubitril/Valsartan 49 mg/51 mg film-coated tablets. The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

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

Study 1: single dose Sacubitril/Valsartan 24 mg/26 mg, fasted conditions

Design

A single-dose, randomised, two-period, two-treatment, crossover bioequivalence study was carried out under fasted conditions in 74 healthy male subjects, aged 18-49 years. Each subject received a single dose (24 mg/26 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 two dosing periods, separated by a washout period of six days.

Blood samples were collected pre-dose and at 0.083, 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 24 and 48 hours after administration of the products.

The design of the study is acceptable.

Sacubitril and valsartan may be taken without reference to food intake. Therefore, 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

74 subjects were enrolled in the study. One subject withdrew due to personal reasons after completion of period I and before study drug administration in period II. 73 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sacubitril, 24 mg/26 mg under fasted conditions.

Treatment N=73	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	552 ± 214	555 ± 214	546 ± 275	0.50 (0.33 - 4.00)
Reference	546 ± 250	548 ± 250	565 ± 300	0.50 (0.33 - 4.00)

***Ratio (90% CI)**	1.03 (1.00 – 1.06)	-	0.99 (0.89 – 1.10)	-

$AUC_{0-\infty}$	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, 24 mg/26 mg under fasted conditions.

Treatment N=73	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	5557 ± 2088	5879 ± 2039	977 ± 379	1.50 (0.67 - 4.00)
Reference	5696 ± 2187	6027 ± 2159	1047 ± 384	1.50 (0.67 – 4.00)
***Ratio (90% CI)**	0.93 (0.88 – 0.99)	-	0.93 (0.86 – 0.99)	-

$AUC_{0-\infty}$	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*

Study 2: single dose Sacubitril/Valsartan 97 mg/103 mg, fasted conditions

Design

A single-dose, randomised, two-period, two-treatment, crossover open label bioequivalence study was carried out under fasted conditions in 74 healthy male subjects, aged 18-48 years. Each subject received a single dose (97 mg/ 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 two dosing periods, separated by a washout period of six days.

Blood samples were collected pre-dose and at 0.083, 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 24 and 48 hours after administration of the products.

The design of the study is acceptable.

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

74 subjects were enrolled in the study. One subject withdrew before drug administration in period II due to personal reasons. 73 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sacubitril, 97 mg under fasted conditions.

Treatment N=73	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1964 ± 687	1986 ± 690	1635 ± 725	0.67 (0.33 - 5.00)
Reference	2008 ± 786	2030 ± 790	1840 ± 1040	0.67 (0.33 – 4.00)
***Ratio (90% CI)**	0.99 (0.96 – 1.03)	-	0.94 (0.84 – 1.05)	-

$AUC_{0-\infty}$	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 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of valsartan, 103 mg under fasted conditions.

Treatment N=73	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	15984 ± 8124	16510 ± 8205	2941 ± 1458	1.75 (0.50 - 5.00)
Reference	15377 ± 7618	15859 ± 7736	2762 ± 1391	1.75 (0.67 – 4.00)
***Ratio (90% CI)**	1.04 (0.94 – 1.13)	-	1.06 (0.95 – 1.19)	-

$AUC_{0-\infty}$	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 studies 1 and 2</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 studies Sacubitril/Valsartan 24 mg/26 mg and 97 mg/103 mg is considered bioequivalent with Entresto 24 mg/26 mg and 97 mg/103 mg.

The results of study 2 conducted for the 97 mg/103 mg strength can be extrapolated to the 49 mg/51 mg strength, 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 (version RMP.NUS.104878 (4.0)-6024.01, 22 April 2025), 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.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	Embryo-foetal toxicity/lethality
Important potential risks	Cognitive impairment Neonatal/infantile toxicity through exposure from breast milk
Missing information	Long term use in heart failure patients

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. On request the MAH has included specific adverse drug reaction follow-up questionnaires FUQs for 'Cognitive impairment' in annex 4 of the RMP.

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 two bioequivalence studies 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.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, EU/1/15/1058. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sacubitril/Valsartan 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets have 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 with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 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
NL/H/6035/001-3/II/001	Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier • Introduction of a manufacturer of the active substance supported by an ASMF	No	5-12-2025	Approved	N/A