LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sanpla
(sacubitril (as sacubitril sodium), valsartan (as valsartan disodium))

SE/H/2686/001-003/DC

This module reflects the scientific discussion for the approval of Sanpla. The procedure was finalised at 2026-03-04. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Sanpla, 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg, Film-coated tablet.

The active substance is sacubitril (as sacubitril sodium) and valsartan (as valsartan disodium). A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II receptor blockers (ARBs), other combinations, ATC code: C09DX04

Mechanism of action

Sacubitril/valsartan exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits of sacubitril/valsartan in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodelling.

The indications and posology are in line with the centrally authorised reference product and are not further discussed.

II.2 General comments on the submitted dossier

The application for Sanpla, 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, CZ, EL, HR, HU, PL, SI and SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Entresto, 24 mg/26 mg, film-coated tablet, authorised in EU since 2015, with Novartis Europharm Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Entresto, 97 mg/103 mg, film-coated tablet,

from Germany with Novartis Europharm Limited as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted study has been provided. The clinical facility was inspected by the FDA in 2021 and 2023, without any critical findings. The bioanalytical facility was inspected by the FDA in 2024, without any critical findings. The clinical and the bioanalytical facilities were inspected by the Spanish authority (AEMPS) in 2023. There were critical findings, but these are not considered to affect the reliability of the current study. No issues regarding GCP have been identified during the assessment of the submitted bioequivalence study. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of sacubitril/valsartan are well known. As sacubitril/valsartan is a widely used, well-known active substances, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The applicant has provided an ERA document which is in line with the 2024 ERA-GL;
The relevant reference ERA were conducted for Entresto by Novartis. The Entresto ERA (dated 2015) uses PEC values based on the highest possible Fpen of 0.01 and the estimated PECsw for sacubitril and for valsartan were higher than the trigger value of 0.01 μg/L, requiring a phase II risk assessment.

All relevant Phase II tier A were conducted in the reference ERA for sacubutril and valsartan, including the sediment-dweller toxicity study according to OECD TG218, (formerly belonging to Phase II Tier B ERA) as well as PECsw and adsorption parameters in OECD 106, now mandatory under Phase II Tier A assessment. Sacubutril and valsartan are not expected to pose any risk to STP, surface water, groundwater, sediment or soil compartments.

Valsartan and sacubitril have low potential for bioaccumulation (log Dow < 3) thus, evaluation of secondary poisoning is not required. Valsartan and sacubitril are not considered to be PBT, nor vPvB substances.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Sanpla (Sacubitril/Valsartan) with the reference product Entresto.

Pharmacokinetic properties of the active substances
Absorption: Following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolised to the active metabolite sacubitrilat (LBQ657). These reach peak plasma concentrations in 2 hours, 1 hour, and 2 hours, respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be more than 60% and 23%, respectively.

Following twice daily dosing of sacubitril/valsartan, steady-state levels of sacubitril, LBQ657 and valsartan are reached in three days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates 1.6-fold. Administration with food has no clinically significant impact on the systemic exposures of sacubitril, LBQ657 and valsartan. Sacubitril/valsartan can be administered with or without food.

Linearity: The pharmacokinetics of sacubitril, LBQ657 and valsartan were approximately linear over a sacubitril/valsartan dose range of 24 mg sacubitril/26 mg valsartan to 97 mg sacubitril/103 mg valsartan.

Elimination: Sacubitril, LBQ657 and valsartan are eliminated from plasma with a mean elimination half-life (t½) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

Study C1B03122

Methods

This was a two-treatment, four-period, two-sequence, fully replicate single-dose crossover study conducted in 44 healthy volunteers, comparing Sacubitril/Valsartan, 97 mg/103 mg, film-coated tablet with Entresto, 97 mg/103 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of sacubitril and valsartan were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 17 Jul 2023 and 06 Aug 2023.

Results

The results from the pharmacokinetic and statistical analysis are presented below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for sacubitril, n=85.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**2.837 ± 0.739**	**2.715 ± 1.334**	**0.500 (0.250-2.000)**
Reference	**2.859 ± 0.809**	**2.520 ± 1.394**	**0.500 (0.250-3.500)**
***Ratio (90% CI)**	**99.68 (97.14-102.29)**	**109.86 (100.06-120.61)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for valsartan, n=85.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**31.226 ± 13.108**	**5.468 ± 1.922**	**1.500 (1.000-3.000)**
Reference	**31.858 ± 14.045**	**5.389 ± 2.101**	**1.750 (1.000-4.500)**
***Ratio (90% CI)**	**98.83 (91.88-106.29)**	**101.87 (94.70-109.58)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both sacubitril and valsartan.

A biowaiver was sought for the additional strengths of 24 mg/26 mg and 49 mg/51 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and ICH M13A Guideline on bioequivalence for immediate-

release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical method was adequately validated.

Based on the submitted bioequivalence study, Sanpla is considered bioequivalent with Entresto.

Absence of studies with the additional strengths of 24 mg/26 mg and 49 mg/51 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics is linear in the dose range of 24 mg sacubitril/26 mg valsartan to 97 mg sacubitril/103 mg valsartan.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH (RMS and all CMS): Bausch Health Ireland Limited

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System including all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted an updated 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 Sanpla.

The MAH has submitted the version 0.2 RMP dated 14 Aug 2025 and proposed the following summary safety concerns:

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
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

Note: The safety concerns have been identified based on published list of safety concerns of the reference product Entresto available in the EMA website (RMP Version 9.0, dated 15-Nov-2024).

The proposed RMP is in line with the reference product.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed if the list of important risks and missing information is updated as requested above.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 14 Aug 2025 is considered acceptable.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Sanpla, is found adequate. There are no objections to approval of Sanpla, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments:

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

The package leaflet 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 PlL was English.
The results show that the package leaflet 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. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-