CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Bidcor 24 mg/26 mg film-coated tablets
Bidcor 49 mg/51 mg film-coated tablets
Bidcor 97 mg/103 mg film-coated tablets

(sacubitril sodium/valsartan disodium)

ES/H/0943/001-003/DC

Date: 19 March 2025

This module reflects the scientific discussion for the approval of Bidcor 24mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets. The procedure was finalised at 13 March 2025. For information on changes after this date please refer to the module "Update".

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bidcor 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg film-coated tablets from Laboratorios Alter S.A.

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

Paediatric heart failure:
Bidcor is indicated in children and adolescent aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The drug products are:
- 24/26 mg: a white, oblong, biconvex film-coated tablet containing 24 mg of Sacubitril and 26 mg of Valsartan.
- 49/51 mg: a white, oblong, biconvex film-coated tablet containing 49 mg of Sacubitril and 51 mg of Valsartan.
- 97/103 mg: a white, oblong, biconvex film-coated tablet containing 97 mg of Sacubitril and 103 mg of Valsartan.

The packaging material intended for the commercial use consists in Polyamide/Aluminium /PVC/ blisters.

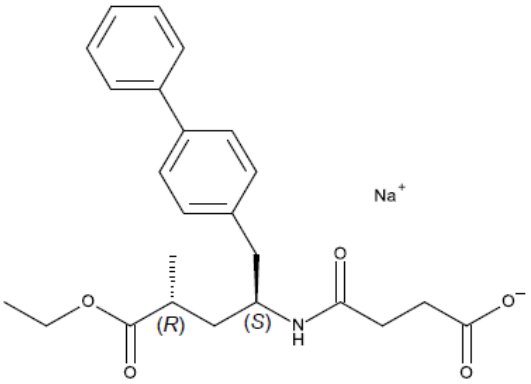
II.2 Drug Substances

SACUBITRIL SODIUM
An ASMF procedure is used to support the quality of the drug substance sacubitril sodium.

General Information

Nomenclature:
INN: Sacubitril sodium
Chemical name: Sodium 4-[(2S,4R)-1-(1,1ô-biphenyl-4-yl)-4-ethoxycarbonyl-4-methylbut-2-yl]ami-no-4-oxobutanoate
CAS number: [149690-05-1]

Chemical structure:



Molecular formule: $C_{24}H_{28}NNaO_5$
Molecular mass: 433.47 g/mol

General Properties:
- Physical description: Almost white to yellow powder.
- Solubility: Freely soluble in water and in absolute ethanol, sparingly soluble in dichloromethane.
- Higroscopicity: The substance is very hygroscopic.
- Isomerism: Sacubitril structure shows two chiral centers which lead to four optical isomers.
- Polymorphism: The active substance shows polymorphism.

Manufacture, in process controls and characterization
Manufacturing process is described with enough detail. Specifications of starting materials and other used in the synthesis are adequate. Impurities which can have influence in the quality of the active substance are defined and controlled. Acceptance criteria in the critical steps of the synthesis are considered appropriate. Information on intermediates and their control is adequate.

Specification, analytical procedures and batch analysis
Specifications of active substance are considered adequated and limits justified.
Analytical methods are correctly described. Their validation is carried out according to IOCH.
Analytical results of batches grant a consistent production of the active substance.

Container closure system
Active substance is packaged in a transparent LDPE bag placed in an aluminium foil bag in a fibre drum. Election of the container closure system is justified. Compliance with the relevant Ph.Eur. monograph and EU Regulation on food contact materials is demonstrated.

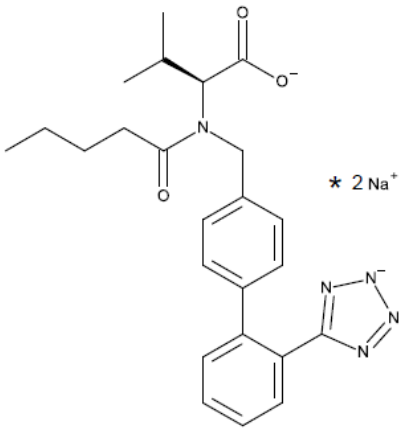
Stability
Stability studies have been carried out according to in force legislation. Protocol, parameters and analytical methods are adequate. Container closure system used in the stability studies is similar to that proposed for storage. Retest period and storage conditions are justified.

VALSARTAN DISODIUM
An ASMF procedure is used to support the quality of the drug substance valsartan disodium.

General Information
Nomenclature:
INN: Valsartan disodium

Chemical name: N-pentanoil-N-[p-(o-1H-Tetrazol-5-ylphenyl)benzyl]-L-valine, disodium salt
CAS number: [391230-93-6]

Chemical structure:



Molecular formule: $C_{24}H_{27}N_5Na_2O_3$
Molecular mass: 435.52 g/mol

General Properties:
- Physical description: Off-white to yellow powder.
- Solubility: Freely soluble in water and in absolute ethanol, practically insoluble in dichloromethane.
- Higroscopicity: The substance is deliquescent.
- Isomerism: Valsartan disodium structure shows one chiral center which lead to two optical isomers.
- Polymorphism: The active substance is amorphous.

Manufacture, in process controls and characterization
Manufacturing process is described with enough detail. Specifications of starting materials and other used in the synthesis are adequate. Impurities which can have influence in the quality of the active substance are defined and controlled. Acceptance criteria in the critical steps of the synthesis are considered appropriate. Information on intermediates and their control is adequate.

Specification, analytical procedures and batch analysis
Specifications of active substance are considered adequated and limits justified.
Analytical methods are correctly described. Their validation is carried out according to IOCH.
Analytical results of batches grant a consistent production of the active substance.

Container closure system
Active substance is packaged in a transparent LDPE bag placed in an aluminium foil bag in a fibre drum. Election of the container closure system is justified. Compliance with the relevant Ph.Eur. monograph and EU Regulation on food contact materials is demonstrated.

Stability
Stability studies have been carried out according to in force legislation. Protocol, parameters and analytical methods are adequate. Container closure system used in the stability studies is similar to that proposed for storage. Retest period and storage conditions are justified.

II.3 Medicinal Product

Description of the product

- 24/26 mg: a white, oblong, biconvex, scored in one side film-coated tablet, containing 24 mg of Sacubitril and 26 mg of Valsartan.
- 49/51 mg: a white, oblong, biconvex, unscored film-coated tablet, containing 49 mg of Sacubitril and 51 mg of Valsartan.
- 97/103 mg: a white, oblong, biconvex, scored in one side film-coated tablet, containing 97 mg of Sacubitril and 103 mg of Valsartan.

The qualitative composition of the finished product is as follows:
Tablet core: Sacubitril sodium, Valsartan disodium, Microcristalline cellulose, Hdroxypropylcellulose, Crospovidone, Silica colloidal anhidrous, Talc, Magnesium stearate.
Coating: Hypromellose, Titanium dioxide, Triacetin.

The packaging material intended for the commercial use consists in Polyamide/Aluminium /PVC/ blisters.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.
The choice of dissolution method is considered appropriate. The information presented supports the proposed quality control dissolution method.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.
Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin.

Scientific data and/or certificates are presented to guarantee compliance with the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents* for these excipients.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in Polyamide/Aluminium /PVC/ blisters. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 36 months.

Storage conditions: This medicinal product does not require any special storage conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects

From the point of view of the chemical and pharmaceutical quality part, a marketing authorization can be granted for the product.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of sacubitril and valsartan are well known. As sacubitril and valsartan are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Publicly available endpoints of the relevant studies have been shared with the Applicant. Sacubitrilat and valsartan are not a PBT, nor vPvB substances. Considering the data, neither sacubitrilat nor valsartan are not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sacubitril/valsartan is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has submitted one bioequivalence study with the 97 mg/103 mg strength according to the *Guideline on the investigation of bioequivalence*, which is discussed below.

IV.2 Pharmacokinetics

Biowaiver

This application concerns three strengths, i.e., 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg film-coated tablets and the bioequivalence study has been carried out with the 97 mg/103 mg strength. The criteria according to the Guideline on the Investigation of Bioequivalence for waiving the 24 mg/26 mg and 49 mg/51 mg tablets are fulfilled as:

- All strengths are manufactured with the same process.
- The qualitative composition of all strengths is the same.

- The composition of the strengths is quantitatively proportional.
- Appropriate dissolution profiles between the different strengths have confirmed to be similar.

Bioequivalence studies

Study code: UECHUP-SACVAL /22-4). EUDRA CT number: 2022-002288-31

GCP compliance
The study was conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and analytical facilities
Clinical site: Clinical Trial Unit, Hospital Universitario de La Princesa. C/ Diego de León, nº62. Madrid, Spain.
Analytical centre: Laboratorios Anapharm Europe S.LU. C/ Encurny 22. Barcelona, Spain

Design.
A randomised, single-dose, two-treatment, two-period, two sequence, crossover full replicate bioequivalence study was carried out under fasted conditions in 36 healthy male/female subjects, aged 19-44years. Each subject received a single dose (97 mg/103 mg tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 7 days.

Analytical and statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
36 subjects were included in the study. *36* subjects were treated, 35 subjects completed all study periods and 36 were used in the statistical analysis according to the protocol.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Table 1. Pharmacokinetic parameters for sacubitril (non-transformed values; arithmetic mean ± SD, t_{max} median, range). N=36. ANOVA

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-Đ}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	2122.65 ±569.47	2137.0 ±573.49	1768.43 ±860.37	0.75 (0.33-6.00)
Reference	2093.19 ±560.84	2100.13 ±531.04	1719.88 ±832.36	0.75 (0.33-5.00)
***Ratio (90% CI)**	100.95 (**98.43-103.54**)	NR	101.45 (**91.20-112.84**) [$]	-
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.				

	AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-Đ}$	Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-Đ}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

**ln-transformed values*

Table 2. Pharmacokinetic parameters for valsartan (non-transformed values; arithmetic mean ± SD, t_{max} median, range). N=36.

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-Đ}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	21710.85± 8954.59	22102.58±8951.83	3414.47±1366.65	1.67 (1.00-5.00)
Reference	21797.88±7920.62	22195.66±7958.08	3439.38±1544.76	1.67 (1.00-5.00)
***Ratio (90% CI)**	97.71 (**88.69-107.64**)	NR	96.99 (**88.09-106.78**) $	-

AUC_{0-t}	Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-Đ}$	Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-Đ}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

**ln-transformed values*

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Bidcor film coated tablets is considered bioequivalent with Entresto.

IV.3 Pharmacodynamics/Clinical efficacy/Clinical safety

No original studies were submitted. This is acceptable in the context of a generic application, and no additional PD, efficacy or safety studies are deemed necessary. The efficacy and safety of sacubitril and valsartan have been demonstrated in several clinical trials conducted with the reference product and during post-marketing experience. Therapeutic indications proposed for Bidcor 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg film-coated tablets are the same as those authorized for the reference product.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan (version 0.2, 16 July 2024), 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 Bidcor 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypotension - Renal impairment - Hyperkalemia - Angioedema - Embryo-fetal toxicity/lethality
Important potential risks	- Neonatal/infantile toxicity through exposure from breast milk - Hepatotoxicity - Cognitive impairment

	- Statin drug-drug interaction - Long-term effects on growth, bone growth and mineralization in the pediatric population
Missing information	- Long-term use of LCZ696 in HF patients - Use in ACEI/ARB naive HF patients

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
-Hypotension	To communicate the risk of hypotension and to reduce the risk of clinically significant hypotension. SmPC: Section 4.2, 4.4, 4.5, 4.8 and 4.9 PL: Sections 2, 3 and 4	-None
-Renal impairment	To communicate the risk of renal impairment and to reduce the risk ofclinically significant renal impairment. SmPC: Section 4.2, 4.4, 4.5 and 4.8. PL: Sections 2, 3 and 4	-None
-Hyperkalemia	To communicate the risk of hyperkalemia and to reduce the risk of clinically significant hyperkalemia. SmPC: Section 4.2, 4.4, 4.5 and 4.8. PL: Sections 2, 3 and 4	-None
-Angioedema	To communicate the risk ofangioedema and to reduce the risk of clinically significant angioedema. SmPC: Section 4.2, 4.3, 4.4, 4.5 and 4.8. PL: Sections 2 and 4 Follow up questionnaire	-None
-Embryo-fetal toxicity/lethality	To communicate the risk of teratogenicity, embryofetotoxicity and embryo-fetal lethality, protect unborn children from exposure to LCZ696. SmPC: Section 4.3 and 4.6. PL: Section 2	-None
Important Potential Risks		
-Neonatal/infantile toxicity through exposure from breast milk	To communicate the potential risk of ADRs in breastfed newborns/infants. SmPC: Section 4.6 PL: Section 2	-None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
-Hepatotoxicity	To communicate the risk of hepatotoxicity from LCZ696 use, especially in patients with hepatic impairment. SmPC: Section 4.2, 4.3, 4.5 and 5.2 PL: Sections 2 and 4	-None
-Cognitive impairment	To convey the relevant findings from clinical and preclinical studies. SmPC: Section 5.1 and 5.3 PL: None.	-None
-Statin drug-drug interaction	To warn about the risks associated with concomitant use of LCZ696 and statins. SmPC: Section 4.5. PL: Section 2	-None
-Long-term effects on growth, bone growth and mineralisation in the pediatric population	To convey the relevant findings from preclinical and clinical studies. SmPC: 5.3	-None
Missing Information		
-Long-term use of LCZ696 in HF patients	Currently available data do not support the need for risk minimization for long-term use in HF patients.	-None
-Use in ACEI/ARB naïve HF patients	To recommend caution by using a lower starting dose of LCZ696 when treating ACEI/ARB naive HF patients due to limited experience in clinical trials. SmPC: Section 4.2. PL: None	-None

- Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the MAH.

There are specific adverse reaction follow-up questionnaires following the reference medicinal product, in order to collect further data to help further characterize and/or closely monitor each of the respective safety concerns:

- Angioedema
- Hepatotoxicity
- Statin-related events
- Cognitive impairment

IV.5 Discussion on the clinical aspects

Please see section IV.2.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Entresto 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg film-coated tablets (Parent PIL-1) and Couldina con Ibuprofeno comprimidos efervescentes (Parent PIL-2). Entresto 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg film-coated tablets (Parent PIL-1) was used for key safety messages, and Couldina con Ibuprofeno comprimidos efervescentes (Parent PIL-2) was used for design and layout. The bridging report submitted by the applicant has been found acceptable.

Based on the above justification the daughter PIL is considered comparable with the parent PILs and assessed as readable in compliance with Articles 59(3) and 61(1) of Directive 2001/83/EC as amended.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product sacubitril/valsartan is found adequate. There are no objections to the approval of Bidcor film coated tablets 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.

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