Medicines Evaluation Board

Public Assessment Report
Scientific discussion

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

NL/H/6082/001-003/DC

Date: 24 July 2026

This module reflects the scientific discussion for the approval of Arnoriam 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, film-coated tablets. The procedure was finalised on 29 October 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 Arnoriam 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, film-coated tablets, from Egis Pharmaceuticals Plc.

The product is indicated for:

- Adult heart failure
  Arnoriam is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.
- Paediatric heart failure
  Arnoriam 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) by Novartis Europharm Limited since 19 November 2015.

The concerned member states (CMS) involved in this procedure were Germany, Greece, France, Italy, Spain and Portugal

II. QUALITY ASPECTS

II.1 Introduction

Arnoriam are white or almost white, oval, biconvex film-coated tablets. The product is odourless or almost odourless. The film-coated tablets of the different strengths can be distinguished by their size and debossing as follows:

Arnoriam 24 mg/26 mg film-coated tablets
The film-coated tablets are stylised with an “E” sign and 651 code on one side and no sign on the other side. The approximate tablet dimensions are 9.5 mm × 4.5 mm. Each film-coated tablet contains 24.3 mg of sacubitril (as sacubitril tromethamine) and 25.7 mg of valsartan (as valsartan tromethamine potassium dihydrate) as active substances.

Arnoriam 49 mg/51 mg film-coated tablets
The film-coated tablets are stylised with an “E” sign and 652 code on one side and no sign on the other side. The approximate tablet dimensions are 12.5 mm × 6.5 mm. Each film-coated tablet contains 48.6 mg of sacubitril (as sacubitril tromethamine) and 51.4 mg of valsartan (as valsartan tromethamine potassium dihydrate) as active substances.

Arnoriam 97 mg/103 mg film-coated tablets
The film-coated tablets are stylised with an “E” sign and 653 code on one side and no sign on the other side. The approximate tablet dimensions are 15.5 mm × 8.0 mm. Each film-coated tablet contains 97.2 mg of sacubitril (as sacubitril tromethamine) and 102.8 mg of valsartan (as valsartan tromethamine potassium dihydrate) as active substances.

The excipients are:
Tablet core - colloidal anhydrous silica (E551), microcrystalline cellulose (E460), crospovidone (E1202), magnesium stearate (E470b), hydrophobic colloidal silica, (E551), low-substituted hydroxypropylcellulose (E463a) and povidone K25 (E1201).

Film coating - macrogol poly(vinyl alcohol) grafted copolymer (E1209), talc (E553), type I glycerol monocaprylocaprate and partially hydrolysed polyvinyl alcohol (E1203).

The three film-coated tablet strengths are dose proportional.

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

II.2 Drug Substance

The active substances are sacubitril tromethamine and valsartan tromethamine potassium dihydrate.

Sacubitril tromethamine
Sacubitril tromethamine is an established active substance not described in the European Pharmacopoeia (Ph.Eur.) The active substance is a crystalline powder and is freely soluble in water. Sacubitril tromethamine exhibits polymorphism, for this product, polymorphic form II is consistently produced.

Manufacturing process
The manufacturing process starts with two starting materials and comprises four chemical transformation steps with three isolated intermediates followed by a salt formation step. The third starting material is introduced in the last step of the synthesis. An organic solvent is used in the last salt formation step. Two catalysts are used in the synthesis. No class 1 solvents 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.

Quality control of the drug substance
The active substance specification is considered adequate to control the quality and is in line with the specification provided by the drug substance manufacturer with additional requirements for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three full-scaled batches.

Stability of the drug substance
Stability data on the active substance have been provided for three production scaled batches in accordance with the applicable European guidelines. Based on the data submitted, a retest period could be granted of 36 months when stored under the stated conditions.

Valsartan tromethamine potassium dihydrate
Valsartan tromethamine potassium dihydrate is an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white powder and is freely soluble in water. Valsartan tromethamine potassium dihydrate exhibits polymorphism, for this product, polymorphic form I is consistently produced.

Manufacturing process
The manufacturing process consists of a salification step and purification of the final active substance. The process starts with valsartan as key intermediate (covered by a CEP). No class 1 organic solvents or heavy metal catalysts 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 the drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur. with additional requirements for particle size distribution and microbiological quality. Batch analytical data demonstrating compliance with this specification have been provided for three full-scaled batches.

Stability of the drug substance
Stability data on the active substance have been provided for three production scaled batches in accordance with the applicable European guidelines. 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 choice of the excipients is justified and their functions explained. The choices of packaging and manufacturing process are adequately justified based on the dosage form. The main development studies performed were the process selection (including the effect of granulation and granulation fluid), particle size distribution, formulation optimisation and manufacturing process development. The development of the QC dissolution method has been adequately justified and the discriminatory power of the method was shown.

Manufacturing process
The main steps in the manufacturing process are granulation, regranulation of dried granules, blending and mixing with the extra granular components, lubrication and mixing and compression followed by film-coating and packaging. The manufacturing process has been validated according to relevant European/ICH 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, except for the film-coating excipients which are controlled via an in-house specification. Tests and acceptance criteria for additional functionality related characteristics for each of the excipients are explicitly laid down in the dossier, unless justified that these characteristics are not relevant for the performance of the drug product. These specifications are acceptable.

Quality control of the drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, mark, colour, identification, dimensions, average mass, uniformity of mass, resistance to crushing, water content, assay, uniformity of dosage units, dissolution, impurities, residual solvents and microbiological quality. Limits in the specification have been justified and are considered appropriate for the adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. A low risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for five commercial batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of the drug product

Stability data on the product have been provided for five full scaled batches (two batches of the 24 mg/26 mg strength, one batch of the 49 mg/51 mg strength and two batches of the 97 mg/103 mg strength) stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Furthermore, photostability studies were performed in accordance with ICH recommendations. The results showed that the product is stable when exposed to light. Based on the data submitted, a shelf life was granted of three years. 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 Arnoriam 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)

At the time of submission of this application, before 1st of September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. At the time of approval the conclusion for this medicinal product was: since Arnoriam 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 tromethamine and valsartan tromethamine potassium dihydrate 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 one bioequivalence study and a biowaiver, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted one bioequivalence study in which the pharmacokinetic profile of the test product Arnoriam 97 mg/103 mg, film-coated tablets (Egis Pharmaceuticals Plc, Hungary) was compared with the pharmacokinetic profile of the reference product Entresto 97 mg/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 following general requirements must be met where a waiver for additional strength is claimed:

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

Dissolution studies were performed in accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

The dissolution tests at pH 4.5 and 6.8 show for the test and reference product that more than 85% of the active substances was dissolved after 15 minutes. At pH 1.2, dissolution was very low for both compounds (≤ 5%). The figures show that the dissolution profiles are similar. The comparability of the dissolution profiles can be accepted also at pH 1.2 without further analyses. Therefore, the profiles can be considered as similar. As all conditions for the biowaiver criteria are met, the biowaiver can be approved for the lower strengths 24 mg/26 mg and 49 mg/51 mg.

Bioequivalence studies

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, full replicate crossover bioequivalence study was carried out under fasted conditions in 46 healthy male subjects, aged 18-49 years. Each subject received a single dose (97 mg sacubitril and 103 mg valsartan) of one of the two sacubitril/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 seven days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.3, 1.5, 1.7, 2, 2.3, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. According to the SPC, the product may be administered with or without food. The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended.

Sacubitril and valsartan may be administered without reference to food intake. From the literature it is known that food does not interact with the absorption of sacubitril and 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 Rev. 1/ Corr ** 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
Two subjects withdrew for personal reasons: one subject before study drug administration in period II and the other subject before study drug administration in period IV. A total of 45 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=45	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	1967 ± 529	1986 ± 530	1676 ± 627	0.5 (0.3 – 4.0)
Reference	1962 ± 531	1989 ± 530	1531 ± 685	0.7 (0.3 – 4.0)
***Ratio (90% CI)**	100.8 (98.5 – 103.2)	-	111.6 (103.3 – 120.6	-

$AUC_{0-\infty}$	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 t = 48 hours
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=45	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	19230 ± 7298	19661 ± 7382	3361 ± 1196	1.5 (0.3 – 4.0)
Reference	20059 ± 8871	20578 ± 8850	3393 ± 1446	1.7 (0.7 – 4.0)
***Ratio (90% CI)**	99.4 (90.7 – 109.0)	-	103.3 (92.4 – 115.5)	-

$AUC_{0-\infty}$	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 t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 80 – 125. Based on the submitted bioequivalence study Arnoriam 97 mg/103 mg is considered bioequivalent with Entresto 97 mg/103 mg.

The results of study MC-0287 with the 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 **.

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 Arnoriam. At the time of approval, the most recent version of the RMP was version 0.4 with sign date off 29 August 2025.

Table 3. 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 mineralisation in the paediatric population
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. At the day 70 assessment, the MAH was requested to have specific adverse drug reaction follow-up questionnaires (FUQ) for the adverse drug reactions (ADRs) 'Angioedema', 'Hepatotoxicity', 'Statin drug-drug interaction' and 'Cognitive impairment' in place in line with the innovator product Entresto. At day 120, The FUQs were in line with those of Entresto. The inclusion of these four FUQs is accepted.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Entresto. 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 Hungarian.

The test consisted of: a pilot test with four participants, followed by two rounds with 10 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

Arnoriam 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, based on the data submitted, considered that essential similarity has been demonstrated for Arnoriam with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 October 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/6082/001-002/IA/1324/G	Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size. Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance - Up to 10-fold increase compared to the originally approved batch size. Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier).	No	12-3-2026	Approved	N/A
NL/H/6082/001-003/IB/002	Change in the (invented) name of the medicinal product - for Nationally Authorised products.	Yes	15-6-2026	Approved	N/A