COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rosuvastatine Sandoz 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets (rosuvastatin calcium)

NL/H/6528/001-004/DC

Date: 6 January 2026

This report reflects the scientific discussion for the approval of Rosuvastatine Sandoz 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets. The procedure was finalised on 28 October 2016 in Portugal (PT/H/1259/001-004/DC). After a transfer on 4 November 2025, the current RMS is the Netherlands. As a result, the product name, procedure number and layout have been updated in this report. For information on other changes after the finalisation 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 agreed in granting a marketing authorisation for Rosuvastatine Sandoz 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets, from Sandoz B.V.

Rosuvastatine Sandoz is indicated for:

- **Treatment of hypercholesterolaemia**
  Adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.
  Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

- **Prevention of Cardiovascular Events**
  Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

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

This decentralised application concerns a generic version of a HMG-CoA reductase inhibitor, Rosuvastatin Calcium, under Rosuvastatine Sandoz (NL/H/6528/001-004/DC), trade name. In this Report, the name Rosuvastatin is used.

The originator product is Crestor, 5 mg, 10 mg, 20 mg and 40 mg, Film-coated Tablets by AstraZeneca UK Limited, authorised in the UK in 21-03-2003 and in Portugal in 23-04-2003.

With the Netherlands as the Reference Member State in this decentralized procedure, Sandoz B.V. is applying for the Marketing Authorizations for:
- Rosuvastatine Sandoz 5 mg, 10 mg, 20 mg and 40 mg, Film-coated Tablets, in Austria, Belgium, Cyprus, France, Germany, Greece, Ireland, Norway and Spain.

The marketing authorization was granted on 26-08-2016 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph and the Marketing Authorisation Holder is Sandoz B.V.

II. QUALITY ASPECTS

II.1 Introduction

Film-coated tablet

Rosuvastatine Sandoz 5 mg film-coated tablets
Brown, round, film-coated tablets with a diameter of 5 mm.

Rosuvastatine Sandoz 10 mg film-coated tablets
Brown, round, film-coated tablets, with a diameter of 7 mm, with “RSV 10”debossed on one side.

{ Rosuvastatine Sandoz 20 mg film-coated tablets}
Brown, round, film-coated tablets, with a diameter of 9 mm, with “RSV 20”debossed on one side.

Rosuvastatine Sandoz 40 mg film-coated tablets}
Brown, round, film-coated tablets, with a diameter of 11 mm, with “RSV 40”debossed on one side.

The other excipients are:

Tablet contents:
Anhydrous lactose, colloidal anhydrous silica, microcrystalline cellulose, maize starch, talc, sodium stearyl fumarate

Tablet coat:
Hypromellose, mannitol (E421), macrogol 6000, talc, titanium dioxide (E171), yellow ferric oxide (E172), red ferric oxide (E172)

Rosuvastatine Sandoz 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets are available in:

- OPA_Al-PVC/Al blister: 7, 10, 14, 20, 21, 28, 30, 40, 42, 50, 60, 70, 84, 90, 98, 100 film-coated tablets
- HDPE bottles with PP cap and silica gel desiccant: 28, 30, 50, 84, 90, 100 film-coated tablets

Not all pack sizes may be marketed

II.2 Drug Substance

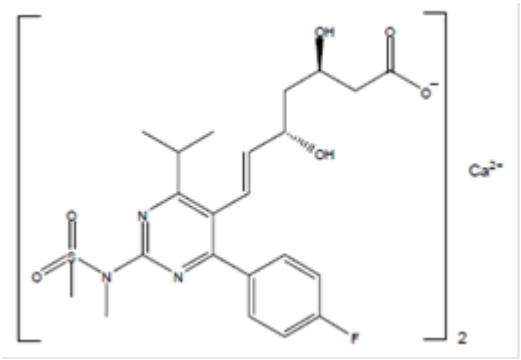
Rosuvastatin calcium is not described in BP or USP. A Ph.Eur. monograph for rosuvastatin calcium has recently been adopted and will be included in Ph.Eur. 8.4 (implemented per 1 April 2015).

General Information

Nomenclature

INN name:	Rosuvastatin Calcium
Chemical name:	Calcium (3R,5S,E)-7-(4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enoate 6-Heptenoic acid, 7-(4-(4-fluorophenyl)-6-(1-methyl)-2-(methyl(methylsulfonyl)amino)-5-pyrimidinyl)3,5-dihydroxy-, calcium salt, (3R,5S,6E) Calcium (3P,5S,6E)-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoat
CAS number:	287714-41-4 Rosuvastatin 147098-20-2 Rosuvastatin Calcium

Structure



The drug substance has two chiral centres, which are positioned at heptanoate chain on carbon atoms 3 and 5, respectively. The absolute configuration at position 3 is R and at position 5 is S.

Molecular formula

Rosuvastatin:	$C_{22}H_{28}FN_3O_6S$
Rosuvastatin Calcium:	$C_{44}H_{54}CaF_2N_6O_{12}S_2$

Relative molecular mass:

Rosuvastatin:	481.54 g/mol
Rosuvastatin Calcium:	1001.14 g/mol

General properties

Description

Almost white or yellowish-white powder

pH
6.7 – 6.9 (1% w/v, 20ºC)

pKa
4.6

Specific optical rotation
The characteristic angle of specific optical rotation (c = 0.5, 589 nm, 20 °C) of rosuvastatin calcium drug substance is between + 14.0 ° and + 20.0 ° (calculated to the anhydrous and solvent free substance).

Solubility
Rosuvastatin calcium is sparingly soluble in distilled water, methanol and ethanol, soluble in acetone and acetonitrilo and freely soluble in dimethylsulfoxide (DMSO) and dimethylformamide (DMF)

Hygroscopicity
Rosuvastatin Calcium is hygroscopic at RH = 90 %, 6 % water absorption.

Chirality
The drug substance has two chiral centres, which are positioned at heptanoate chain on carbon atoms 3 and 5, respectively. The absolute configuration at position 3 is *R* and at position 5 is *S*.

Isomerism
Rosuvastatin diastereoisomer (3S,5S) is a potential impurity, which may be present in Rosuvastatin calcium drug substance. The level of rosuvastatin diastereoisomer (3S,5S) is regularly controlled by HPLC analytical method for related substances/degradation products

Polymorphism
According to the literature no anhydrous crystalline form of rosuvastatin calcium salt has been known up to now. Crystalline Rosuvastatin Ca is known only in the form of hydrate, which can be prepared applying special conditions of precipitation (Pat. Appl. WO 00/42024). Rosuvastatin Calcium manufactured by Lek is amorphous.
Typical X-ray powder diffractogram (XRPD) of drug substance is enclosed. The test has been carried out on the batch A04695603I (ARAZV 1120/07).

<u>Manufacturing process</u>
The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Rosuvastatine Sandoz (NL/H/6528/001-004/DC), are of sufficient quality in view of the present European regulatory requirements.

<u>Quality control of drug substance</u>
The control tests and specifications for drug substance product are adequately drawn up.

Stability of drug substance
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.
The proposed retest period of 2 years when the drug substance is stored at a temperature up to 25°C in an airtight container, under nitrogen, protected from moisture and light, for the manufacturer I is justified.
The proposed retest period of 2 years when the drug substance is stored at 2 – 8°C, for the manufacturer II, is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.

Manufacturing process
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 16 batches. The batch analysis results show that the finished products meet the specifications proposed.

Quality control of drug product
The control tests and specifications for drug product are adequately drawn up.

Stability of drug product
The conditions used in the stability studies are according to the ICH stability guideline. The proposed shelf-life of 24 months when store in the original package for the drug product is considered acceptable.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of rosuvastatin are well known. As rosuvastatin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Rosuvastatin is administered at a maximal dose of 40.0 mg.
From its Experimental log P 0.13 persistence in the environment can not be assumed for the parent compound.
No information is available about the potential of this product to produce adverse environmental effects. Risk of environment impact cannot be excluded.
A disposal advice has been added to the SmPC.

III.2 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the application, the applicant has submitted one single dose bioequivalence study performed with the 40 mg strength at fasted state.

IV.2 Pharmacokinetics

Biowaiver
To request a waiver for the dosage forms of 5, 10 and 20mg, the applicant presented dissolution profiles of all the dosage forms compared with the biobatch formulation of 40mg, at pH levels of 1.2, 4.5 and 6.8. All the dissolution profiles are similar. Therefore a waiver could be granted for the dosage forms of 5, 10 and 20mg.

Bioequivalence studies:
Based on the submitted bioequivalence study Rosuvastatina 1APharma 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets is considered bioequivalent with Crestor 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets

IV.3 Risk Management Plan

The MAH has submitted a Risk Management Plan - Version 02 – April 2014, 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 Rosuvastatine Sandoz 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets.

Summary table of safety concerns as approved in RMP

Important identified risks	• Skeletal muscle effect (myalgia, myopathy, rhabdomyolysis) • Liver effects (increased hepatic transaminases) • Race effects • Increased systemic exposure of Rosuvastatin during concomitant use of protease inhibitors • Renal effects (proteinuria, haematuria) • Diabetes Mellitus • Interstitial lung disease
Important potential risks	None
Missing information	• Use in paediatric population

Risk minimization measures:

- Skeletal muscle effect (myalgia, myopathy, rhabdomyolysis)
  Reference is given in sections 4.2 “Posology and method of administration”, 4.3 “Contraindications”, 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects” of the Global Core Data Sheet.

- Liver effects (increased hepatic transaminases)
  Reference is given in sections 4.2 “Posology and method of administration”, 4.3 “Contraindications”, 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects” of the Global Core Data Sheet.

- Race effects
  Reference is given in sections 4.2 “Posology and method of administration”, 4.3 “Contraindications”, 4.4 “Special warnings and precautions for use” and 5.2 “Pharmacokinetic properties” of the Global Core Data Sheet.

- Increased systemic exposure of Rosuvastatin during concomitant use of protease inhibitors
  Reference is given in sections 4.2 “Posology and method of administration”, 4.3 “Contraindications”, 4.4 “Special warnings and precautions for use” and 4.5 “Interaction with other medicinal products and other forms of interaction” of the Global Core Data Sheet.

- Renal effects (proteinuria, haematuria)
  Reference is given in sections 4.2 “Posology and method of administration”, 4.3

"Contraindications", 4.4 "Special warnings and precautions for use", 4.8 "Undesirable effects" and 5.2 "Pharmacokinetic properties" of the Global Core Data Sheet.

- Diabetes Mellitus
- Reference is given in sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the Global Core Data Sheet.

- Interstitial lung disease
  Reference is given in sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the Global Core Data Sheet.

- Use in Paediatric population
  Reference is given in sections 4.2 "Posology and method of administration" and 4.4 "Special warnings and precautions for use" of the Global Core Data Sheet.

IV.4 Discussion on the clinical aspects

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorized medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

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 Rosuvastatin 5, 10, 20 and 40 mg film-coated tablets, DCP number: PT/H/0247-0249/001-004/DC. The bridging report submitted by the applicant has been found acceptable.

The layout of the leaflet for Rosuvastatin 5, 10, 20 and 40 mg film-coated tablets is identical with the layout of the already successfully tested leaflet for Rosuvastatin 5, 10, 20 and 40 mg film-coated tablets in 2009.

In the present case of Rosuvastatin Sandoz 5, 10, 20 and 40 mg film-coated tablets readability is assured by using the package leaflet for Rosuvastatin Sandoz 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets, for which an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC was performed during PT/H/0247-0249/001-004/DC in 2009

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Rosuvastatine Sandoz 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

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
PT/H/1259/001-4/IB/001	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	22-7-2016	Approved	N.A.
PT/H/1259/001-4/IB/002/G	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 - Other variation Changes in the manufacturing process of the active substance - Minor change to the restricted part of an Active Substance Master File.	No	8-9-2016	Approved	N.A.
PT/H/1259/001-4/IA/006	Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients	Yes	7-3-2017	Approved	N.A.

PT/H/1259/001-4/IB/003	Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	No	9-3-2017	Approved	N.A.
PT/H/1259/001-4/IA/007/G	Change in the name and/or address of the marketing authorisation holder -Change in the location of the administrative offices	Yes	14-4-2017	Approved	N.A.
PT/H/1259/001-4/IA/008	Change in the shape or dimensions of the pharmaceutical form - Immediate release tablets, capsules, suppositories and pessaries	Yes	3-5-2017	Approved	N.A.
PT/H/1259/001-4/IB/009	Change in the (invented) name of the medicinal product - for Nationally Authorised products	Yes	17-6-2017	Approved	N.A.
PT/H/1259/001-4/WS/004	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	11-1-2018	Approved	N.A.
PT/H/1259/001-4/WS/005	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	No	11-1-2018	Approved	N.A.

	- Introduction of a manufacturer of the active substance supported by an ASMF				
PT/H/1259/001-4/IA/010/G	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)). Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance - Addition of a new specification parameter to the specification with its corresponding test method Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	Yes No Yes	29-1-2019	Approved	N.A.
PT/H/1259/001-4/IA/013	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient	No	29-4-2019	Approved	N.A.

	- European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph: - New certificate from an already approved manufacturer				
PT/H/1259/001-4/IB/012	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC - Implementation of wording agreed by the competent authority	Yes	11-6-2019	Approved	N.A.
PT/H/1259/001-4/IB/014	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan - Update of risk management plan (RMP) for Rosuvastatin, version 3.0, dated 26 Oct 2018. RMP has been updated to version 3.1, dated 08-07-2019	No	4-10-2019	Approved	N.A.
PT/H/1259/001-4/II/018	Change in manufacture of the active substance - other variation: an update of ASMF	No	13-10-2020	Approved	N.A.
PT/H/1259/001-4/IA/019/G	Change in the name and/or address of the marketing authorisation holder	Yes	11-11-2020	Approved	N.A.
PT/H/1259/001-4/IB/015	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the	Yes	24-12-2020	Approved	N.A.

	assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC - Implementation of wording agreed by the competent authority				
PT/H/1259/001-4/IB/016	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC - Implementation of wording agreed by the competent authority	Yes	24-12-2020	Approved	N.A.
PT/H/1259/001-4/IB/011	Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	No	25-12-2020	Approved	N.A.
PT/H/1259/001-4/IA/017/G	Change in test procedure for the finished product - Minor changes to an approved test procedure Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph:	No	11-3-2021	Approved	N.A.

	- New certificate from an already approved manufacturer - Updated certificate from an already approved manufacturer				
PT/H/1259/002-3/IA/021	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process.	No	8-4-2021	Approved	N.A.
PT/H/1259/001-4/IB/020	Change in the (invented) name of the medicinal product - for Nationally Authorised products: change of tradename in DE	Yes	10-5-2021	Approved	N.A.
PT/H/1259/001-4/IB/022/G	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)). Changes in the manufacturing process of the active substance - other variation Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place Submission of a new or updated Ph. Eur. certificate of suitability or deletion of	Yes No No No	1-7-2021	Approved	N.A.

	Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph: - Updated certificate from an already approved manufacturer Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	No			
PT/H/1259/001-4/R/001	Renewal	No	12-8-2021	Approved	N.A.
PT/H/1259/001-4/IB/024	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance - Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	Yes	24-9-2021	Approved	N.A.
PT/H/1249/001-4/IB/025	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance - Deletion of a non-significant	No	19-11-2021	Approved	N.A.

	specification parameter (e.g. deletion of an obsolete parameter)				
PT/H/1259/001-4/IB/023	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC - Implementation of wording agreed by the competent authority	Yes	9-12-2021	Approved	N.A.
PT/H/1259/001-4/IA/031/G	Change in the name and/or address of the marketing authorisation holder	Yes	29-3-2022	Approved	N.A.
PT/H/1259/001-4/IA/027	Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	No	6-4-2022	Approved	N.A.
PT/H/1259/001-4/IB/026	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	14-4-2022	Approved	N.A.
PT/H/1259/001-4/IB/030	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of	Yes	22-6-2022	Approved	N.A.

	Regulation 1901/2006SmPCSmPC - Implementation of wording agreed by the competent authority				
PT/H/1259/001-4/IB/028/G	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 - Changes to quality control testing arrangements for the active substance- replacement or addition of a site where batch control/testing takes place	No	2-7-2022	Approved	N.A.
	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Secondary packaging site - Primary packaging site - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.	No			
	Change in the batch size (including batch size ranges) of the finished product - More than 10-fold increase compared to the originally	No			

	approved batch size for immediate release (oral) pharmaceutical forms Change in control of the Finished Product - Other variation Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) - Change that does not affect the product information Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change of specification(s) of a former non-EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/active substance starting material	 No No No			
PT/H/1259/001-4/WS/032	Change to in-process tests or limits applied during the manufacture of the finished product - Other variation: Change of test for blister packaging	No	6-8-2022	Approved	N.A.
PT/H/1259/001-4/IA/033	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/interme-diate used in the	No	21-9-2022	Approved	N.A.

	manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph: - Deletion of certificates (in case multiple certificates exist per material)				
PT/H/1259/001-4/IA/034	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)).	Yes	15-1-2023	Approved	N.A.
PT/H/1259/001-4/WS/029	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan - Updated RMP	No	6-3-2023	Approved	N.A.
PT/H/1259/001-4/IA/035	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation	Yes	26-5-2023	Approved	N.A.
PT/H/1259/001-4/IA/039	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) - All other	No	8-12-2023	Approved	N.A.
PT/H/1259/001-4/IA/036	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to	No	27-9-2025	Approved	N.A.

	the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
PT/H/1259/001-4/WS/037	Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier. - Re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	No No	18-3-2024	Approved	N.A.
PT/H/1259/001-4/IA/040/G	Change in the name and/or address of the marketing authorisation holder	Yes	30-3-2024	Approved	N.A.
PT/H/1259/001-4/IA/041/G	Change in the name and/or address of the marketing authorisation holder	Yes	22-11-2024	Approved	N.A.
PT/H/1259/001-4/IA/038	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product	No	4-12-2024	Approved	N.A.

	- Minor change in the manufacturing process.				
PT/H/1259/001-4/IA/043	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)).	Yes	19-1-2025	Approved	N.A.
PT/H/1259/001-4/IB/042	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	3-2-2025	Approved	N.A.
PT/H/1259/001-4/IA/044/G	Change in the name and/or address of the marketing authorisation holder	Yes	9-6-2025	Approved	N.A.
PT/H/1259/001-4/IA/045/G	Change in the name and/or address of the marketing authorisation holder	Yes	12-11-2025	Approved	N.A.