COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezetimibe/Atorvastatine Viatris 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg, film-coated tablets (ezetimibe and atorvastatin calcium trihydrate)

NL/H/5764/001-004/DC

Date: 30 July 2025

This module reflects the scientific discussion for the approval of Ezetimibe/Atorvastatine Viatris 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg, film-coated tablets. The procedure was finalised on 12 February 2024. 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 Ezetimibe/Atorvastatine Viatris 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg, film-coated tablets from Viatris Limited.

The product is indicated for:
Prevention of Cardiovascular Events
Ezetimibe/Atorvastatine Viatris is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Hypercholesterolaemia
Ezetimibe/Atorvastatine Viatris is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate.

- patients not appropriately controlled with a statin alone
- patients already treated with a statin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)
Ezetimibe/Atorvastatine Viatris is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein (LDL) apheresis).

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 a European Reference Product (ERP), Atozet 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets from MSD Sharp & Dohme B.V., which has been registered in Germany via decentralised procedure (DE/H/3895/001-004/DC) since 12 September 2014.

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

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe/Atorvastatine Viatris 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg are film-coated tablets. The four strengths of the film-coated tablets can be distinguished by shape, size and color and are as follows:

Ezetimibe/Atorvastatine Viatris 10 mg/10 mg
White, round, biconvex film-coated tablets, with a diameter of approximately 8.1 mm. Each tablet contains 10 mg of ezetimibe and 10 mg of atorvastatin (as calcium trihydrate) as active substances.

Ezetimibe/Atorvastatine Viatris 10 mg/20 mg
White, ovaloid, biconvex film-coated tablets, with dimensions approximately 11.6 x 7.1 mm. Each tablet contains 10 mg of ezetimibe and 20 mg of atorvastatin (as calcium trihydrate) as active substances.

Ezetimibe/Atorvastatine Viatris 10 mg/40 mg
White, capsule shaped, biconvex film-coated tablets, with dimensions approximately 16.1 x 6.1 mm. Each tablet contains 10 mg of ezetimibe and 40 mg of atorvastatin (as calcium trihydrate) as active substances.

Ezetimibe/Atorvastatine Viatris 10 mg/80 mg
Yellow, oblong, biconvex film-coated tablets, with dimensions approximately 19.1 x 7.6 mm. Each tablet contains 10 mg of ezetimibe and 80 mg of atorvastatin (as calcium trihydrate) as active substances.

The excipients are:
Tablet core - cellulose microcrystalline 101, mannitol, calcium carbonate, croscarmellose sodium, hydroxypropylcellulose LV, polysorbate 80, iron oxide yellow (E172), magnesium stearate, povidone K29/32 and sodium laurilsulfate.
Film-coating 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg film-coated tablets - lactose monohydrate, hypromellose 2910, titanium dioxide (E171) and macrogol 4000.
Film-coating 10 mg/80 mg film-coated tablets - hypromellose 2910, titanium dioxide (E171), talc, macrogol 400 and iron oxide yellow (E172).

The drug product corresponds to a film-coated tablet intended for immediate release containing two active substances, atorvastatin calcium trihydrate and ezetimibe in separate layers in the same dosage form. The layers are manufactured separately. The ezetimibe layer remains the same at the different strengths, however the atorvastatin layer varies at the different strengths and is weight proportional.

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

II.2 Drug Substance

The active substances are ezetimibe and atorvastatin calcium trihydrate.

Ezetimibe
Ezetimibe is a white to off-white crystalline powder, which is freely soluble in ethanol and methanol but practically insoluble in water. The drug substance exhibits polymorphism. . Ezetimibe contains three asymmetric carbon atoms and therefore exhibits optical isomerism. For this product, a specific polymorphic form is consistently produced and adequately

controlled. Ezetimibe is not described in the Ph.Eur. An USP monograph on ezetimibe is available.

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

Manufacturing process

Site 1: The manufacturing process consists of a regulatory synthesis route. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Site 2: The manufacturing process consists of a synthesis compromised in three stages, with a total of six synthetic steps and one purification step. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the USP. Batch analytical data demonstrating compliance with this specification have been provided for three batches from each ASMF-holder.

Stability of drug substance

Site 1: Stability data on the active substance have been provided for three lower scale and seven higher scale validation batches and one micronized batch, stored at long-term conditions up to 60 months and accelerated conditions up to 6 months. Based on the data submitted, a retest period could be granted of 48 months when stored under the stated conditions

Site 2: Stability data on the active substance have been provided in the ASMF. Based on the data submitted, a retest period could be granted of 36 months when stored under the stated conditions.

Atorvastatin calcium trihydrate

The active substance atorvastatin calcium trihydrate is an established active substance described in the European Pharmacopoeia (Ph.Eur.). Atorvastatin calcium trihydrate has two chiral centres and therefore exhibits optical isomerism. The active substance is a crystalline powder and is very slightly soluble in water. For this product, polymorphic form I is consistently produced.

The CEP procedure is used for the active substance atorvastatin calcium trihydrate with two different CEP-holders. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for six batches by site 1 and three batches by site 2.

Stability of drug substance

Site 1: The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

Site 2: The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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 development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, formulation development, dissolution methods development, manufacturing process development and the performance of comparative dissolution studies at three pHs complementary to the bioequivalence study carried out on ezetimibe/atorvastatin 10 mg/80 mg strength and in support of the biowaiver of strengths claimed for the additional 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg strengths.. The provided comparative dissolution data support the requested biowaiver.
Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process of Ezetimibe/Atorvastatine Viatris, film-coated tablets, which includes manufacturing of atorvastatin blend (dispensing, mixing, binder solution preparation, wet granulation, drying, sizing, mixing, lubrication), manufacturing of ezetimibe blend (dispensing, mixing, binder solution preparation, wet granulation, wet milling, drying, sizing,

sieving, mixing, sieving/lubrication), tablet formation (tabletting, coating suspension preparation), coating and packaging, is considered to be a standard process.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for one pilot scale batch and two commercial scale batches per strength in accordance with the relevant European guidelines.

Control of excipients

Specifications for all excipients have been provided. Except for coating agents, the specifications for all other excipients are in line with Ph. Eur., with additional testing for some excipients. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests or appearance, average weight, disintegration time, content uniformity, identification, identification of colourants, water content, dissolution, assay, related substances and microbiological tests. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from twelve batches (two commercial scale and one smaller scale per strength) from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for twelve batches (two commercial scale batches and one smaller scale batch per strength) stored at 25°C/ 60% RH (36 months), 30°C/ 60% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions needed to be included in the SmPC or on the label.

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 Ezetimibe/Atorvastatine Viatris 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)

Since Ezetimibe/Atorvastatine Viatris 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 Atozet 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

Ezetimibe and atorvastatin calcium trihydrate are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ezetimibe/Atorvastatine Viatris 10 mg/80 mg, film-coated tablets (Viatris Limited, Ireland) was compared with the pharmacokinetic profile of the reference product Atozet 10 mg/80 mg, film-coated tablets (MSD Sharp & Dohme B.V., Germany).

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

For the additional strengths (Ezetimibe/Atorvastatine 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg) a biowaiver is claimed, based on the following general requirements (according to the EMA Bioequivalence guideline):

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The pharmaceutical products are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and the composition of the strengths are quantitatively proportional.

The dissolution was investigated according to the EMA Bioequivalence guideline, with comparative dissolution studies at three pHs (pH 1.2, 4.5 and 6.8) complementary to the bioequivalence study. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar. The provided comparative dissolution data support the requested biowaiver.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, open-label, crossover bioequivalence study was carried out under fasted conditions in 80 healthy male (66) and female (14) subjects, aged 19-44 years. Each subject received a single dose (10 mg/80 mg) of one of the two ezetimibe/atorvastatin calcium trihydrate formulations. The tablet was orally administered with 240 ±2 mL water after a fasting period of 10 hours. There were two dosing periods, separated by a washout period of 15 days.

Blood samples were collected pre-dose and at 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Ezetimibe and atorvastatin calcium trihydrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ezetimibe and atorvastatin calcium trihydrate. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with

CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
A total of 8 subjects were withdrawn from the study, all in period 2, 4 subjects withdrew due to adverse events, 3 subjects did not report to the facility and 1 subject was tested positive in drug abuse. 72 subjects were eligible for pharmacokinetic analysis.
The measured pharmacokinetic parameters of total ezetimibe (ezetimibe (unconjugated) + ezetimibe (conjugated)) and atorvastatin calcium trihydrate are summarized below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe (ezetimibe (unconjugated) + ezetimibe (conjugated)), 10 mg under fasted conditions.

Treatment N=72	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	1147 ± 554	-	143 ± 59	0.75 (0.50 - 2.00)
Reference	1190 ± 540	-	164 ± 63	0.75 (0.50 – 4.50)
***Ratio (90% CI)**	0.94 (0.90 – 0.98)	-	0.86 (0.81 – 0.90)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration (t = 72 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 atorvastatin calcium trihydrate, 80 mg under fasted conditions.

Treatment N=72	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	319 ± 198	323 ± 198	92 ± 87	1.33 (0.50 – 4.50)
Reference	323 ± 198	328 ± 198	92 ± 79	1.00 (0.50 – 4.50)
***Ratio (90% CI)**	9.99 (9.47 - 1.05)	-	1.01 (9.15 – 1.11)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration (t = 72 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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25 for both atorvastatin and total ezetimibe. Based on the submitted bioequivalence study Ezetimibe/Atorvastatine Viatris 10 mg/80 mg is considered bioequivalent with Atozet 10 mg/80 mg.

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 Ezetimibe/Atorvastatine Viatris. At the time of approval, the most recent version of the RMP was version 0.1 dated 19 January 2023.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	Muscle injury (Rhabdomyolysis/myopathy) Abnormal liver function
Important potential risks	None
Missing information	Use in children less than 18 years of age Use in patients with moderate or severe liver problems (Exposure in patients with moderate or severe hepatic insufficiency)

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Atozet. No new clinical studies were conducted. 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 English.
The test consisted of: a pilot test with 2 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

Ezetimibe/Atorvastatine Viatris 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Atozet 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets. Atozet is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ezetimibe/Atorvastatine Viatris with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 February 2024.

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/5764/001-4/IB/001	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.	No	16-05-2024	Approved	N.A.
NL/H/5764/001-4/IB/002/G	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 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	Yes Yes	08-08-2024	Approved	N.A.

	1901/2006SmPCSmPC – Other				
NL/H/5764/001-4/IA/003	Change in pack size of the finished product • Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. • Change within the range of the currently approved pack sizes	Yes	28-10-2024	Approved	N.A.
NL/H/5764/001-4/IB/004	Change(s)in the Summary of Product Characteristics, Labelling or Package Leaflet of (union referral procedure) • Other variation	Yes	16-01-2025	Approved	N.A.
NL/H/5764/001-4/IB/005/G	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) 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	No No	01-05-2025	Approved	N.A.

	Tightening of specification limits Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance Minor changes to an approved test procedure Other variation	 No No			
NL/H/5764/001-4/IB/007/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. • Updated certificate from an already approved manufacturer	No No	08-05-2025	Approved	N.A.