COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cholecalciferol STADA Arzneimittel AG 800 IU, 5.600 IU, 10.000 IU, 11.200 IU, 20.000 IU, 25.000 IU and 50.000 IU, soft capsules (cholecalciferol)

NL/H/5523/001-007/DC

Date: 5 December 2024

This module reflects the scientific discussion for the approval of Cholecalciferol STADA Arzneimittel AG 800 IU, 5.600 IU, 10.000 IU, 11.200 IU, 20.000 IU, 25.000 IU and 50.000 IU, soft capsules. The procedure was finalised on 17 May 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

1,25(OH)2D	1,25-dihydroxyvitamin D / calcitriol (metabolite of vitamin D)
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
DBP	Vitamin D binding protein
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
IU	International Unite
MAH	Marketing Authorisation Holder
nmol/L	Nanomol per litre
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
VDR	Vitamin D receptor
WEU	Well-Established Use

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cholecalciferol STADA Arzneimittel AG 800 IU, 5.600 IU, 10.000 IU, 11.200 IU, 20.000 IU, 25.000 IU and 50.000 IU, soft capsules, from Stada Arzneimittel AG.

The product is indicated for:

- Initial treatment of vitamin D deficiency (serum 25(OH)D < 25 nmol/L) in adults and adolescents.
- Prevention of vitamin D deficiency in adults and adolescents with an identified risk.
- As an adjunct to specific therapy for osteoporosis in adult patients with vitamin D deficiency or at risk of vitamin D deficiency.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted via a decentralised procedure pursuant to Article 10a of Directive 2001/83/EC, which concerns a well-established use (WEU) application. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Cholecalciferol in oral dosage forms was first introduced into the European market more than ten years ago. It has been widely marketed and used for the treatment of vitamin D deficiency and has a recognised efficacy and an acceptable level of safety. Bridging data has been submitted to bridge between the proposed drug product and the products used in the used literature. To justify the bridging, *in vitro* studies has been performed demonstrating similarity of the disintegration of the proposed formulation and the already marketed cholecalciferol soft capsules. Similar disintegration times suggest that the active ingredient is effectively presented in the stomach as an immediately available solution.

The concerned member states (CMS) involved in this procedure was Luxembourg. A repeat-use procedure (NL/H/5523/001/E/001-7) has been used to register the product in Belgium.

II. QUALITY ASPECTS

II.1 Introduction

Cholecalciferol STADA Arzneimittel AG are soft capsules that contains contain cholecalciferol as active substance. The soft capsules are presented in the following seven strengths which can be distinguished by colour, shape and size:

- 800 IU: light green, transparent, oval shaped soft gelatin capsule containing a clear

colourless liquid and with dimensions of 9.5 ± 1 mm long x 5.5 ± 1 mm width. Each soft capsule contains 800 IU cholecalciferol (equivalent to 20 micrograms vitamin D_3).

- 5600 IU: light blue, transparent, oval shaped soft gelatin capsule containing a clear colourless liquid and with dimensions of 9.5 ± 1 mm long x 5.5 ± 1 mm width. Each soft capsule contains 5600 IU cholecalciferol (equivalent to 140 micrograms vitamin D_3).
- 10000 IU: dark orange, transparent, oval shaped soft gelatin capsule containing a clear colourless liquid and with dimensions of 9.5 ± 1 mm long x 5.5 ± 1 mm width. Each soft capsule contains 10000 IU cholecalciferol (equivalent to 250 micrograms vitamin D_3).
- 11200 IU: purple, transparent, round shaped soft gelatin capsule containing a clear colourless liquid and with a diameter of 6.5 ± 5 mm. Each soft capsule contains 11.200 IU cholecalciferol (equivalent to 280 micrograms vitamin D_3).
- 20000 IU: reddish orange, transparent, oval shaped soft gelatin capsule containing a clear colourless liquid and with dimensions of 9.5 ± 1 mm long x 5.5 ± 1 mm width. Each soft capsule contains 20000 IU cholecalciferol (equivalent to 500 micrograms vitamin D_3).
- 25000 IU: purple, transparent, oval shaped soft gelatin capsule containing a clear colourless liquid and with dimensions of 9.5 ± 1 mm long x 5.5 ± 1 mm width. Each soft capsule contains 25000 IU cholecalciferol (equivalent to 625 micrograms vitamin D_3).
- 50000 IU: dark blue, transparent, oval shaped soft gelatin capsule containing a clear colourless liquid and with dimensions of 9.5 ± 1 mm long x 5.5 ± 1 mm width. Each soft capsule contains 50000 IU cholecalciferol (equivalent to 1250 micrograms vitamin D_3).

The excipients are:

- 800 IU:
  Capsule content - medium chain triglycerides, butylated hydroxyanisole (E320) and butylated hydroxytoluene (E321).
  Capsule shell - gelatin (E441), glycerol (E422), liquid partially dehydrated sorbitol, FD&C blue (E133) and purified water.
- 5600 IU:
  Capsule content - medium chain triglycerides, butylated hydroxyanisole (E320) and butylated hydroxytoluene (E321).
  Capsule shell - 180 bloom gelatin (E441), glycerol (E422), liquid partially dehydrated sorbitol, FD&C blue (E133) and purified water.
- 10000 IU:
  Capsule content - medium chain triglycerides, butylated hydroxyanisole (E320) and butylated hydroxytoluene (E321).
  Capsule shell - gelatin (E441), glycerol (E422), liquid partially dehydrated sorbitol, FD&C red (E129) and purified water.
- 11200 IU:
  Capsule content - medium chain triglycerides, butylated hydroxyanisole (E320) and

butylated hydroxytoluene (E321).
Capsule shell - 180 bloom gelatin (E441), glycerol (E422), liquid partially dehydrated sorbitol, FD&C blue (E133), FD&C red (E129) and purified water.

- 20000 IU:
  Capsule content - medium chain triglycerides, butylated hydroxyanisole (E320) and butylated hydroxytoluene (E321).
  Capsule shell - gelatin (E441), glycerol (E422), liquid partially dehydrated sorbitol, FD&C red (E129) and purified water.
- 25000 IU:
  Capsule content - medium chain triglycerides, butylated hydroxyanisole (E320) and butylated hydroxytoluene (E321).
  Capsule shell - gelatin (E441), glycerol (E422), liquid partially dehydrated sorbitol, FD&C blue (E133), FD&C red (E129) and purified water.
- 50000 IU:
  Capsule content - medium chain triglycerides, butylated hydroxyanisole (E320) and butylated hydroxytoluene (E321).
  Capsule shell - gelatin (E441), glycerol (E422), liquid partially dehydrated sorbitol, FD&C blue (E133) and purified water.

The soft capsules are packed in white opaque polyvinyl chloride/polyvinylidene dichloride/ Aluminium (PVC/PVDC/Aluminium) blisters.

II.2 Drug Substance

The active substance is cholecalciferol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance are white or almost white crystals, very sparingly soluble in water, soluble in fatty oils, freely soluble in ethanol (96%) and soluble in other organic solvents. No information on potential polymorphism has been reported in the literature. Physical characteristics of particle size and polymorphism have no impact on this formulation as the drug substance is present in solution in the finished product.

The CEP procedure is used for the active substance. 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. and additional requirements of the CEP. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The re-test period of the active substance is 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 choice of excipients is justified and their functions explained. An overage of the active substance is applied. This is adequately justified. Dissolution studies cannot be performed due to the non-aqueous, fatty oil matrix in which the active substance is dissolved, but confirmation has been provided that the dosage form complies with the specification of the Ph. Eur. disintegration test. Disintegration tests are routine tests in the drug product specification.

Manufacturing process

The main steps of the manufacturing process are the preparation of the gelatin mass, preparation of the fill, encapsulation, drying and polishing. The process is a non-standard manufacturing process as the drug unit content is below 2%. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches.

Control of excipients

The excipients, except for the colourants, comply with Ph. Eur. requirements. The colourants, which are listed in the Annex I of EU Directive 94/36/EC, are tested according to in-house specifications. Compliance statements (EU Directives and Regulations) are provided for the colourants. 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 for description, identification and content of cholecalciferol and antioxidants, uniformity of dosage unit, average weight of filled capsules, average net content, uniformity of weight, uniformity of content, disintegration time, chromatographic purity, assay, and microbial quality. 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. Furthermore, a risk assessment for elemental impurities according to ICH Q3D has been submitted for strength 800 IU, 10000 IU, 20000 IU and 50000 IU and were found to be acceptable. The risk assessment process has not identified potential elemental impurities with levels above 30% of the established permissible daily

exposures (PDE). Therefore, no additional controls are required for elemental impurities for this product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data of three exhibit batches per strength, from the proposed production site(s), have been provided demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches of each strength stored at 25°C/ 60% RH (36 months), 30°C /65% RH (36 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies as described in the ICH Q1B were performed and showed that the product is photosensitive. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are 'Do not store above 25°C and store in the original package in order to protect from light'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for the active substance and for the excipient gelatin have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cholecalciferol STADA Arzneimittel AG 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

The MAH has provided a comprehensive and extensive overview of the primary and secondary pharmacodynamics of cholecalciferol.

III.1 Pharmacology

Cholecalciferol is a steroid hormone (secosteroid) produced in the skin, via interaction of 7-dehydrocholesterol (7-DHC), with ultraviolet (UV) irradiation (sunlight), or obtained from dietary sources (Esvelt et al., 1978; How et al., 1994; Olds et al., 2008). The active form of vitamin D_3, i.e. 1,25-dihydroxycholecalciferol (1,25(OH)2D_3 or else calcitriol), plays an important role in maintaining blood calcium (Ca) and phosphorus (P) levels and mineralisation of bone. The activated form of cholecalciferol binds to vitamin D receptor (VDR) and modulates gene expression, leading to an increase in serum Ca concentrations by increasing

intestinal absorption of P and Ca, thereby promoting distal renal tubular reabsorption of Ca and increasing osteoclastic resorption. In addition, vitamin D possesses further pharmacological action in brain, heart, pancreas, mononuclear cells, activated lymphocytes, and skin (Christakos et al., 2016; Lehmann, 2005; PubChem Cholecalciferol).

III.2 Pharmacokinetics

Primary pharmacodynamics

Extensive animal studies have shown that vitamin D is required for normal growth and development (EMA CVMP Vitamin D, 1998). Vitamin D signalling is needed for myocyte function. Despite the low level of VDR protein normally found muscle, deleting myocyte VDR had important effects on muscle size and strength. Maintenance of normal vitamin D signalling is a useful strategy to prevent loss of muscle function and size (Girgis et al., 2019).

Secondary pharmacodynamics

Secondary pharmacology comprises the effects of vitamin D beyond Ca homeostasis, the non-classical effects. The non-classic actions of vitamin D can be categorised into three general effects, i.e. regulation of hormone secretion, regulation of immune function, and regulation of cellular proliferation and differentiation. Because of these effects, ecological and observational studies suggest that low vitamin D status could be associated with higher mortality from life-threatening conditions including cancer, cardiovascular disease (CVD) and diabetes mellitus (Christakos et al., 2016; Hamden et al., 2009; Oinam et al., 1999; PubChem Cholecalciferol; Xin et al., 2017).

III.3 Toxicology

Pre-clinical studies conducted in several animal species have demonstrated that toxic effects occur in animals at doses much higher than those required for therapeutic use in humans. In toxicity studies at repeated doses, the effects most reported were increased calciuria and decreased phosphaturia and proteinuria. Hypercalcaemia has been reported in high doses. In a state of prolonged hypercalcaemia, histological alterations (calcification) were more frequently borne by the kidneys, heart, aorta, testes, thymus and intestinal mucosa (Chavhan et al., 2011; EMA CVMP Vitamin D, 1998; FDA Pharmacology Review Fosamax Plus; Gerhard and Jaffey, 2020; Hsu et al., 2008; Morita et al., 1995). High doses of vitamin D during pregnancy in rabbits have been reported to affect foetal death, maternal Ca and cholesterol homeostasis, and neonatal Ca homeostasis, and to cause calcific aortic lesions in the mother and an apparent dose-related development of supravalvular aortic lesions in the newborn (Chan et al., 1979; Fu et al., 2019). However, at doses equivalent to those used therapeutically, cholecalciferol has no teratogenic activity. Cholecalciferol has no potential mutagenic or carcinogenic activity.

Overall, cholecalciferol does not present any toxicological concern, since toxicity is only observed in exceeding doses far beyond those recommended for administration and therefore not relevant when the product is taken according to the directions laid out in the SmPC.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Cholecalciferol STADA Arzneimittel AG 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.5 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional data on these aspects.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cholecalciferol is a well-known active substance with established efficacy and tolerability. The dossier is based on well-established use of the active substance, no new clinical data was submitted, instead the MAH submitted a clinical overview for the justification of the proposed indications and posology, which includes numerous publications. This is acceptable.

IV.2 Pharmacokinetics

In accordance with part II of Annex I of Directive 2001/83, regarding article 10a applications, the MAH demonstrated using bridging data that the product applied for is similar to the products described in literature. The MAH has provided a well summarised pharmacokinetics overview which is briefly described below. This is sufficient evidence to bridge the statements regarding the pharmacokinetics of cholecalciferol to the proposed formulations.

Absorption

Cholecalciferol is absorbed up to 80% in the small intestine by passive diffusion after incorporation into mixed micelles. Vitamin D_3 absorption occurs not only by passive diffusion, but involves, at least partly, cholesterol transporters. Fat-soluble vitamin D_3 is absorbed through the small intestine in the presence of bile acids with the help of micelle formation and gets into the blood through lymphatic circulation (Compston et al., 1981; PubChem Cholecalciferol; Reboul, 2011; Reboul, 2015). So, the administration with the major meal of the day might therefore facilitate the absorption of vitamin D_3.

Distribution

Following absorption, vitamin D_3 enters the blood as part of chylomicrons and then associates mainly with a specific α-globulin. Vitamin D_3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D_3, the major storage form (Borel et al., 2015; Compston et al., 1981; PubChem Cholecalciferol; Reboul, 2015). Smaller amounts are

distributed to adipose and tissue and stored as vitamin D_3 at these sites for later release into the circulation (Camozzi et al., 2016; Disriksen et al., 2015; Jones, 2008).

Metabolism

Cholecalciferol is rapidly metabolised by hydroxylation in the liver to 25-hydroxyvitamin D_3 and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D_3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D_3 undergoes glucuronidation prior to elimination (Jones et al., 1987; Jones, 2013; PubChem Cholecalciferol).

Elimination

Due to their high lipid solubility, vitamin D_3 and its metabolites are stored in fat deposits for prolonged period and eliminated slowly from the body. Vitamin D_3 has a plasma $t_{½}$ of 19-25 hours and a terminal $t_{½}$ of about 2 months. 25(OH)D_3 has an experimental elimination $t_{½}$ of 15-19 days and the hormone 1,25(OH)2D_3 has a $t_{½}$ of about 15 hours. Cholecalciferol and its metabolites are excreted mainly in the bile and faeces and only to a slight extent via urine; they undergo extensive enterohepatic recirculation. (Jones et al., 1987; PubChem Cholecalciferol).

Pharmacokinetic Interactions

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Concomitant treatment with phenytoin or barbiturates can decrease the effect of vitamin D_3 because of metabolic activation. Concomitant use of glucocorticoids can decrease the effect of vitamin D_3. Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D_3. Drugs leading to fat malabsorption, e.g. orlistat, may impair the absorption of vitamin D_3. The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D_3 activity by inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase. Systemic corticosteroids inhibit the absorption of calcium. Long-term use of corticosteroids may offset the effect of vitamin D_3. Rifampicin may also reduce the effectiveness of vitamin D_3 due to hepatic enzyme induction. Isoniazid may reduce the effectiveness of vitamin D_3 due to inhibition of the metabolic activation of vitamin D_3 (FAO/WHO vitamin D; Holick, 2011; Holick et al., 2011; Marcinowska-Suchowierska et al., 2018; Özkan et al., 2012; PubChem Cholecalciferol; Roth et al., 2018; SmPCs of EU authorised Vitamin D_3 products e.g. Benferol, Disteomin, Fultivit D_3; Whiting et al., 2011).

IV.3 Pharmacodynamics

The pharmacodynamics of cholecalciferol is well-established and has been adequately summarized by the MAH. No new data have been submitted, which is acceptable for this well-established use application.

IV.4 Clinical efficacy

Supplementation with cholecalciferol is to be considered as well-established for prevention and treatment of vitamin D deficiency and as an adjunct to specific therapy for osteoporosis. The Applicant has adequately summarised the bibliographical efficacy data for each proposed indication and posology in the clinical overview.

IV.5 Clinical safety

The safety of cholecalciferol in the proposed indication and posology is considered well-established. The Applicant has adequately summarised the bibliographical safety data in the clinical overview. In general, vitamin D is well tolerated. However, there is a risk for toxicity, especially with higher dosages. Hypercalcaemia and hypercalciuria are the main adverse events. The precautions of use in other special populations are sufficiently addressed in the SmPC.

IV.6 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 Cholecalciferol STADA Arzneimittel AG.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
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.

IV.7 Discussion on the clinical aspects

This procedure concerns a well-established use application for cholecalciferol. For this authorisation, reference is made to literature. No new clinical studies were conducted. The clinical benefit of treating vitamin D deficiency is well known. Supplementation with cholecalciferol is to be considered as well-established for the prevention of vitamin D deficiency in patients at risk, for the treatment of vitamin D deficiency and as an adjunct to osteoporosis therapy. The MAH has adequately summarised the bibliographical efficacy data in the clinical overview.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Fultivit-D_3 800 IU, soft capsules (BE/H/0270/001-3) for content and to Levothyroxine (DE/H/3012-13/001-3) for layout. The

bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cholecalciferol STADA Arzneimittel AG 800 IU, 5.600 IU, 10.000 IU, 11.200 IU, 20.000 IU, 25.000 IU and 50.000 IU, soft capsules, have a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the indications as well as the posology of the new product are in line with current cholecalciferol use and recommendations in the RMS and CMS countries, in which cholecalciferol has been registered for more than ten years. Based upon clinical data and the longstanding clinical experience, the use of cholecalciferol in the proposed indications can be considered well-established with demonstrated efficacy and safety.

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 well-established use has been demonstrated for Cholecalciferol Acure, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 17 May 2023.

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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/5523/ 004/IA/001-7	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	05-12-2023	Approved	N.A.
NL/H/5523/ IB/002/G	- Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location. - Change in the (invented) name of the medicinal product; for Nationally Authorised Products.	No Yes	18-03-2024	Approved	N.A.
NL/H/5523/001/E/001-7	Repeat use application to register the product in Belgium.	No	23-10-2024	Approved	N.A.