COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vitamin D3 Teva 25,000 IU, soft capsules (cholecalciferol)

NL/H/5389/001/DC

Date: 28 November 2022

This module reflects the scientific discussion for the approval of Vitamin D3 Teva 25,000 IU, soft capsules. The procedure was finalised on 28 April 2022. 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
DBP	Vitamin D-binding protein
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IU	International units
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
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 Vitamin D3 Teva 25,000 IU, soft capsules, from Teva B.V.

The product is indicated for the initial treatment of clinically relevant vitamin D deficiency in adults (serum level <25 nmol/L (<10 ng/mL)).

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

The marketing authorisation has been granted via a decentralised procedure under Article 10a of Directive 2001/83/EC (well-established use (WEU) application). Well-established medicinal use needs to be demonstrated for the active substance of the medicinal product for at least 10 years in the specific therapeutic area. In a WEU application, results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. Therefore, no clinical studies have been performed by the marked authorisation holder (MAH) and instead, bibliographical data are submitted.

Cholecalciferol as active substance in medicinal products have been in well-established medicinal use within the Community for more than ten years, with recognised efficacy and an acceptable level of safety.

The concerned member states (CMS) involved in this procedure were Germany and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Vitamin D3 Teva is a yellow, opaque, oval soft gelatin capsule.

Each capsule contains as active substance 25,000 international units (IU) of cholecalciferol (vitamin D3), equivalent to 0.625 mg cholecalciferol.

The capsules are packed in PVC/PVDC/aluminium blister packs.

The excipients are:
Capsule fill – medium-chain triglycerides and all-rac-α-Tocopherol (E307)
Capsule shell – gelatin (E441), glycerol (E422), titanium dioxide (E171), yellow iron oxide (E172), purified water and trace substances of medium-chain triglycerides, lecithin/phosphatidylcholine (from soybean), caprylic/capric triglycerides, ethanol, glyceride (from sunflower seed oil), oleic acid, ascorbyl palmitate and tocopherol.

II.2 Drug Substance

The active substance, cholecalciferol, is an established active substance which is described in the European Pharmacopoeia. The active substance consists of white or almost white crystals which are practically insoluble in water, freely soluble in ethanol, soluble in trimethylpentane and in fatty oils. It is sensitive to air, heat and light. Solutions in solvents without an antioxidant are unstable and are to be used immediately. Issues in regards to polymorphism are not relevant, 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., including those for microbiological testing. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided in accordance with applicable European guidelines demonstrating the stability of the active substance for three batches at long term conditions for 60 months and three batches at accelerated conditions for 6 months. Based on the data submitted, a retest period could be granted of 60 months when stored at 2°C to 8°C.

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, their concentrations and the characteristics that can influence the drug product performance or manufacturability have been discussed. The necessity of the antioxidant all-rac-α-tocopherol has been justified.

The formulation trials to evaluate the choice for a suitable antioxidant and a suitable lipid solvent is acceptable based on screening study results. According to Ph. Eur., cholecalciferol is practically insoluble in water. As the active substance is already dissolved in a fatty oil matrix in the formulation, it is acceptable that no dissolution test was developed. In addition, as cholecalciferol is practically insoluble in water, there is no point in comparing dissolution profiles in physiological pHs, as required in the Bioequivalence Guideline, of the proposed formulation against other cholecalciferol products on the EU market or the products used in literature. Hence, it is acceptable that no dissolution studies are performed. The MAH performed the disintegration test in accordance with Ph. Eur.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. In accordance with the *EMA Guideline on process validation for finished products,* the manufacturing process is considered a non-standard process in view of the low unit content (<2%) of cholecalciferol. Hence, validation data of the proposed commercial scale batches are provided. The soft capsules manufacturing process involves capsule fill mass preparation, capsule shell mass preparation, encapsulation, drying, mechanical sorting, visual sorting, bulk packaging and final packaging into blisters. The description of the manufacture in general is considered sufficient. In-process controls are carried out on the fill material, undyed gelatin preparation, dyed gelatin preparation, during encapsulation, after drying, visual control and packaging control. A holding time of 6 months for the capsules stored in bulk packaging is justified.

Control of excipients

All excipients comply with the current version of the Ph. Eur. except for yellow iron oxide and a band lubricant (*Phosal MCT*) which comply with the United States Pharmacopeia monographs. 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 appearance, filling weight, uniformity of mass, uniformity of dosage units, total mass, disintegration in water, water content of shell, identity and assay of cholecalciferol, identity and assay of tocopherol, assay for pre-cholecalciferol, degradation products/ impurities, microbial purity and identity of colorants. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Batch analytical data from three production scale batches from each of the two production sites have been provided, demonstrating compliance with the specification. An adequate nitrosamines risk evaluation report has been provided. The currently identified potential root causes for presence of nitrosamine impurities (defined in document EMA/409815/2020) have been adequately addressed. No risk for presence of nitrosamines in the drug product was identified. Satisfactory validation data for the analytical methods have been provided.

Stability of drug product

Stability data on the product have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the product for 6 months at accelerated conditions, 12 months at intermediate conditions and 36 months long term conditions. On basis of the data submitted and in view of the absence of any trends besides the increase of water content at all conditions, a shelf-life of 24 months was granted. The labelled storage conditions are "store below 25°C, stored in the original package in order to protect from moisture".

A shelf-life of 6 months is acceptable for the bulk product packed in aluminium pouches. All results were within specification limits following two batches stored at 6 months at long-term conditions. The MAH provided photostability data for the drug product in line with the recommendations in ICH guideline Q1B. The capsules are not sensitive to light.

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

Certificates of suitability issued by the EDQM have been provided for gelatin, which is from animal origin (bovine). 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 Vitamin D3 Teva 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 Pharmacology

The MAH has provided a comprehensive and extensive overview of the primary and secondary pharmacodynamics of cholecalciferol. The primary pharmacodynamics included the mechanism of action (including actions that do not directly influence gene expression), (vitamin D-regulated) bone formation, vitamin D-regulated chondrocyte differentiation and function, vitamin D-regulated bone resorption and other direct or indirect effects on bone. Secondary pharmacodynamics included mechanisms in the skin, vitamin D receptor (VDR) polymorphisms and its effects on type I and type II diabetes and VDR's relation to vascular disease. It was noted that the MAH paid a lot of attention to the secondary pharmacodynamic effects of vitamin D in diabetes. The relation with autoimmunity was more extensively described by the MAH, including a description of the direct effects of

vitamin D on the immune system (e.g. regulating T-cell functionality) and the hematopoietic system in general. It is endorsed that no safety pharmacodynamics studies related to (direct) effects of vitamin D on vital organs nor pharmacodynamic drug interaction studies are available. The clinical body of evidence also does not suggest acute effects on vital organs. For a well-established use procedure, the overview of pharmacology data to support the mode of action and proof-of-concept of cholecalciferol is adequate.

III.2 Pharmacokinetics

The MAH has provided a brief overview of the pharmacokinetic parameters of vitamin D, including information on absorption, distribution, metabolism and excretion of vitamin D, drug interactions (with cholestyramine, anticonvulsant drugs, corticosteroids and calcitonin) and other relevant studies. The MAH provided a literature overview of non-clinical studies and also some pharmacokinetics literature data in humans, which is a summary of the information provided in the pharmacokinetics section of the clinical overview. The overview is considered adequate. The absence of pharmacokinetic drug interaction study data can be endorsed, because this information is provided in the clinical overview.

III.3 Toxicology

The MAH has provided a clear overview of the toxicology of cholecalciferol, which was based on up-to-date literature. This included single dose and repeat-dose toxicity in animal studies. The MAH also provided some literature-based toxicology data in humans, including a discussion on the safety data of the excipients. It is agreed with the MAH that there are no indications of carcinogenic potential for cholecalciferol. In contrast, there is some evidence in animal models of cancer that vitamin D may act as anti-neoplastic factor. The MAH has also provided an overview of the reproductive and developmental toxicity of vitamin D based on literature. The toxicology information provided is considered adequate.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The MAH has provided a brief justification that ERA studies are not needed for their cholecalciferol product, because drug products with the same formulation (i.e. soft capsule), dose and dose regimen already exist on the market. Therefore, it is likely that the current product will not lead to increased environmental exposure but rather results in substitution of an existing market share. The absence of a complete ERA is acceptable.

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 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

Cholecalciferol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

In this bibliographic application procedure, the MAH did not submit any new clinical data, but instead showed that the information on pharmacokinetics, pharmacodynamics, efficacy and safety as described in the submitted literature is applicable to the proposed formulation.

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.

Absorption

Due to the fat soluble characteristics of vitamin D, the absorption process in the intestines is more efficient in the presence of biliary salts and when dietary fat is present in the lumen of the small intestine (Grossmann & Tangpricha, 2010; Borel et al., 2015; Martindale, 2020).
EFSA (2016) considers that the average absorption of vitamin D from a usual diet is about 80%. The vitamin D absorbed from the intestine is incorporated into chylomicrons that reach the systemic circulation through the lymphatic system (EFSA, 2016).

Table 1 – Synonyms and abbreviations used for vitamin D and its metabolites

Name/ abbreviation	Equivalent to
Vitamin D3	Cholecalciferol; D3
Vitamin D2	Ergocalciferol
25(OH)D	25(OH)D3; Calcifediol; 25-hydroxy-cholecalciferol; 25-hydroxy-vitamin D3; (In the group of calcidiols)
25(OH)D2	25-hydroxyvitamin D2; (In the group of calcidiols)
1α(OH)D3	Alfacalcidol; 1α-hydroxycholecalciferol (In the group of calcidiols)
1,25(OH)2D	1,25(OH)2D3;

	1,25-dihydroxy-cholecalciferol; 1,25-dihydroxy-vitamin D3; (In the group of calcitriols)
1,25(OH)2D2	1,25-dihydroxyergocalciferol; (In the group of calcitriols)

Trang et al. (1998) compared the ability of vitamin D2 and D3 to elevate serum 25(OH)D (calcifediol, a metabolite of vitamin D3), finding that the increase in serum 25(OH)D concentrations was 70% greater (1.70 times) with vitamin D3 than the increase obtained with vitamin D2. Armas et al. (2004) showed note that a higher dose vitamin D2 should be considered equivalent to vitamin D3 (50,000 IU of vitamin D2 versus 15,000 IU or even 5,000 IU of vitamin D3). There are few studies directly comparing the pharmacokinetics of 25-hydroxycholecalciferol (25(OH)D3) to cholecalciferol (D3). Increases in 25(OH)D to steady state plasma concentration were about three times as effective in the 25(OH)D3 groups than in the D3 group (Graeff-Armas et al., 2020).

Distribution

Vitamin D and its metabolites circulate in the blood bound to a specific α-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of ultraviolet light (Martindale, 2020). Within hours of ingestion or synthesis in the skin, vitamin D is distributed to the liver for conversion (hydroxylation) or delivered as either vitamin D or its metabolites to the storage tissues. 25(OH)D is taken up from the blood into tissues, probably by protein-binding (EFSA, 2016).

Metabolism

In general, the liver and other tissues metabolise vitamin D, whether from the skin or oral ingestion, to 25(OH)D, the principal circulating form of vitamin D, by several enzymes of which CYP27A1 (mitochondrial) and CYP2R1 (microsomal) are the best studied. 25(OH)D is then further metabolised to 1,25(OH)2D principally in the renal proximal tubule by the enzyme CYP27B1 (Bikle et al., 2012). 1,25(OH)2D is the principal hormonal form of vitamin D, responsible for most of its biologic actions. 25(OH)D and 1,25(OH)2D are hydroxylated to form 24,25(OH)2D and 1,24,25 (OH)3D, respectively. This 24-hydroxylation is generally the first step in the breakdown (catabolism) of these active metabolites. CYP24A1 is induced by 1,25(OH)2D, which serves as an important feedback mechanism to avoid vitamin D toxicity. The vitamin D metabolites are transported in blood bound to vitamin D-binding protein (DBP) and albumin. Very little circulates as the free form (Bikle et al., 2012).

It was initially thought that both vitamin D2 and vitamin D3 follow the same metabolic pathway. However, minor differences in the chemistry between the two forms of vitamin D result in differences in the site of hydroxylation and leads to the production of unique biologically active metabolites (Houghton et al., 2006).

Saleh et al. (2017) investigated the effect of a high dose of vitamin D3 on circulating concentrations of 25(OH)D3 and its metabolites in healthy individuals with self-perceived

fatigue and vitamin D insufficiency (in this case defined as 25(OH)D3 <50 nmol/L). It was concluded that administration of a single high dose of vitamin D3 leads to a significant increase in concentrations of metabolites. Due to the high inter-individual variation in the 25(OH)D3 response to supplementation, any given dose of vitamin D is unlikely to achieve optimal vitamin D status in all treated individuals (Saleh et al., 2017).

The liver produces DBP and albumin and these proteins may be lost in protein-losing enteropathies or the nephrotic syndrome. Thus individuals with liver, intestinal, or renal diseases that result in low levels of these transport proteins may have low total levels of the vitamin D metabolites without being vitamin D deficient as their free concentrations may be normal (Bikle et al., 2012).

Elimination

Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some reuptake in the intestines of vitamin D that has been excreted in the bile (enterohepatic recycling), but it is considered to have a negligible contribution. Certain vitamin D substances may be distributed into breast milk (Martindale, 2020). There are two main pathways of degradation, the C23 lactone pathway, and the C24 oxidation pathway (EFSA, 2016). Blood levels of 25(OH)D3 represent a balance between its formation rate and clearance by several oxidative and conjugative processes.

Special patient groups

Vitamin D deficiency is common in patients with end stage renal disease on dialysis, but little is known about 24,25(OH)2D3 metabolite production in the kidneys of this patient group. Some authors report that the CYP24A1 enzyme is upregulated in chronic kidney disease, but reports of low serum levels of 24,25(OH)2D3 in these patients bring this into question. Lack of substrate or increased clearance of the metabolite have been proposed as possible causes. Graeff-Armas et al. (2018) concluded that the enzymatic activity of CYP24A1 is abnormal in end stage renal patients on dialysis.

Single, large dose of cholecalciferol

Data from studies have shown that a single large dose of vitamin D raises calcidiol concentrations and a decrease was shown in parathyroid hormone after a single dose of 100,000 IU cholecalciferol (vitamin D3) in an elderly population (Ilahi et al., 2008). Trivedi et al. (2003) showed a decrease in fractures with dosing of 100,000 IU cholecalciferol every four months.

Overall, the pharmacokinetics are adequately summarised by the MAH and a bridge between the MAH's product and the different products used in the submitted literature has been established.

IV.3 Pharmacodynamics

In the body, vitamin D2 and D3 are converted to the main circulating forms called calcidiols (25(OH)D2 or 25(OH)D3). It can be transformed into the biologically active metabolites called calcitriols (1,25(OH)2D2 or 1,25(OH)2D3) (EFSA, 2016).

Calcitriol augments absorption and retention of calcium (Ca^{2+}) and phosphate. Although regulation of Ca^{2+} homeostasis is considered to be its primary function, accumulating evidence underscores the importance of calcitriol in a number of other processes. Calcitriol acts to maintain normal concentrations of Ca^{2+} and phosphate in plasma by facilitating their absorption in the small intestine, by interacting with parathyroid hormone to enhance their mobilisation from bone and by decreasing their renal excretion. It also exerts direct physiological and pharmacological effects on bone mineralisation. The mechanism of action of calcitriol is mediated by its interaction with the VDR. Calcitriol binds to cytosolic VDRs within target cells, and the receptor-hormone-complex translocates to the nucleus and interacts with DNA to modify gene transcription. The VDR belongs to the steroid and thyroid hormone receptor superfamily. Calcitriol also exerts nongenomic effects. It is controversial whether the presence of a functional VDR is required for this action (Brunton et al., 2011).

The MAH's description of the pharmacodynamics of Vitamin D is acceptable, also considering that it is an endogenous substance.

IV.4 Clinical efficacy

The MAH has adequately discussed the clinical efficacy of cholecalciferol. The bibliographic data showed vitamin D deficiency was resolved or improved as indicated by increases in serum 25(OH)D levels. The MAH submitted and discussed several studies to support: the treatment of vitamin D deficiency, the difference between vitamin D2 and D3 potencies, treatment strategies, special patient groups (including: adolescents, bariatric patients, patients with primary hyperparathyroidism, critically ill patients, patients with chronic kidney disease, pregnancy and newborns) and other. It was not clear how the submitted data should be translated to the proposed dose regimen. However, the proposed posology is acceptable as it is in line with the registered SmPC of Thorens (PT/H/2370/003, Thorens 25,000 IU, hard capsules).

IV.5 Clinical safety

The MAH has adequately discussed the clinical safety of cholecalciferol and has including study data on hypercalcaemia, overdose, contraindications and special warnings, drug interactions and safety in special populations (including: foetal risks, breastfeeding and fertility). Cholecalciferol is usually well tolerated. The main safety concerns are associated with vitamin excess, resulting in hyperphosphatemia or hypercalcaemia. Associated effects of hypercalcaemia include hypercalciuria, ectopic calcification, and renal and cardiovascular

damage (Martindale, 2020). Hypercalcaemia may eventually lead to soft tissue calcification and resultant renal and cardiovascular damage (EFSA, 2016).

Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence, and vertigo. Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin administration should be stopped if toxicity occurs. Mild asymptomatic hypercalcaemia will usually resolve if calcium and other contributory drugs such as vitamin D are stopped. It has been stated that vitamin D dietary supplementation may be detrimental in persons already receiving an adequate intake through diet and exposure to sunlight, since the difference between therapeutic and toxic concentrations is relatively small. The most patent forms of vitamin D, such as alfacalcidol and calcitriol, might reasonably be expected to pose a greater risk of toxicity; however, their effects are reversed rapidly on withdrawal (Martindale, 2020).

Hypersensitivity reactions have occurred according to the literature; skin irritation or contact dermatitis has been reported with topical preparations (Martindale, 2020). The active metabolite of vitamin D (calcitriol) can cause allergic reactions. Hypersensitivity to calcitriol was reported, the hormonally active metabolite of vitamin D (Unal et al., 2016). Other (rare) reports of hypersensitivity or idiosyncratic reactions include pruritus (Reginster et al., 2005; Den Uyl et al., 2010) and rash (Reginster et al., 2005). There are a limited number of studies on chronic spontaneous urticaria and their results are inconsistent (Tuchinda et al., 2018).

The safety profile is adequately described and is reflected 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 Vitamin D3 Teva 25,000 IU, soft capsules.

Table 2 – 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

The clinical benefit of treating vitamin D deficiency is well known. The bibliographic data showed vitamin D deficiency was resolved or improved as indicated by increases in serum calcidiol levels. The MAH discussed several studies to support the efficacy and safety of

initial treatment of vitamin D deficiency with cholecalciferol. No new clinical studies were conducted. The proposed indication is widely used and known and sufficiently discussed in the provided literature and therefore acceptable.

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 first round with ten participants, followed by a second round with ten participants, as no changes were made to the PL. 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

Vitamin D3 Teva 25,000 IU, soft capsules has a proven chemical-pharmaceutical quality. The product has an adequate efficacy and safety profile and is considered widely established.

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, have granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 April 2022.

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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
N/A	N/A	N/A	N/A	N/A	N/A