COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Colecalciferol 1A Pharma 800 IU, 3200 IU, 25,000 IU, and 50,000 IU, soft capsules (cholecalciferol)

## NL/H/5471/001-004/DC

## Date: 5 January 2023

**This module reflects the scientific discussion for the approval of Colecalciferol 1A Pharma 800 IU, 3200 IU, 25,000 IU, and 50,000 IU, soft capsules. The procedure was finalised at 31 August 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

| | |
|---|---|
| 1,25(OH)2D | 1,25-dihydroxyvitamin D / calcitriol (metabolite of vitamin D) |
| 25(OH)D | Calcifediol (metabolite of vitamin D) |
| ASMF | Active Substance Master File |
| BHT | Butylhydroxytoluene |
| 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 |
| LPS | Lipopolysaccharide |
| MAH | Marketing Authorisation Holder |
| NTD | Neural tube defect |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |
| USP | United States Pharmacopoeia |
| VDR | Vitamin D receptor |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Colecalciferol 1A Pharma 800 IU, 3200 IU, 25,000 IU, and 50,000 IU, soft capsules, from 1A Pharma GmbH.

The products' indications are as follows:

800 IU soft capsules

- Treatment of vitamin D deficiency (serum level <25 nmol/L (<10 ng/mL)) in adults and young adults
- Prevention of vitamin D deficiency (serum level <25 nmol/L (<10 ng/mL)) in adults with an identified risk

3200 IU soft capsules

- Treatment of vitamin D deficiency (serum level <25 nmol/L (<10 ng/mL)) in adults and young adults

25,000 IU, and 50,000 IU soft capsules

- Treatment initiation of clinically relevant vitamin D deficiency (serum level <25 nmol/L (<10 ng/mL)) in adults

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

This decentralised procedure concerns a marketing authorisation application in accordance with Article 10a of Directive 2001/83/EC as amended (well-established use (WEU) application). For a WEU 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. In a WEU application, results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

The concerned member state (CMS) involved in this procedure was Belgium.

# II. QUALITY ASPECTS

## II.1 Introduction

Colecalciferol 1A Pharma are soft capsules of the following strengths:

- 800 IU – opaque, light yellow, oval, soft capsules of size 2, each containing 20 µg cholecalciferol (vitamin D3), corresponding to 800 IU
- 3200 IU – opaque, yellow, oval, soft capsules of size 6, each containing 80 µg cholecalciferol (vitamin D3), corresponding to 3200 IU

- 25,000 IU – opaque, white, oval, soft capsules of size 3, each containing 0.625 mg cholecalciferol (vitamin D3), corresponding to 25,000 IU
- 50,000 IU – opaque, red, oval, soft capsules of size 6, each containing 1.25 mg cholecalciferol (vitamin D3), corresponding to 50,000 IU

The soft capsules have different sizes and are packed in opaque PVC/PVdC-Aluminium blisters.

The excipients are:

- Capsule content
  - For all strengths: butylhydroxytoluene (BHT) (E321) and medium chain triglyceride oil.
- Capsule shell
  - For all strengths: gelatin (E-441), glycerol 99,5% (E-422), titanium dioxide (E171) and purified water.
  - Additionally, for 800 IU and 3200 IU: yellow iron oxide (E172).
  - Additionally, for 50,000 IU: red iron oxide (E172).

The 800 IU and 3200 IU strengths are dose proportional. The 25,000 IU, and 50,000 IU strengths are also dose proportional.

## II.2 Drug Substance

The active substance is cholecalciferol (vitamin D3), an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and it is practically insoluble in water, freely soluble in ethanol (96%), and soluble in trimethylpentane and in fatty oils. Polymorphism is not relevant as the finished product is a solution.

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. In addition, a test for microbiological

quality has been included in the drug substance specification. Batch analytical data demonstrating compliance with the specifications have been provided for four batches.

Stability of drug substance

The active substance is stable for three years 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 development of the product has been described, the choice of excipients is justified and their functions explained. The use and quantity of the antioxidant is adequately justified. The indication for use of the lowest strength in the paediatric population has been adequately justified. As the active substance is already dissolved, it is acceptable that no dissolution test was performed on the finished product. In addition, as cholecalciferol is practically insoluble in water, it was not needed to compare dissolution profiles of the proposed formulation against other cholecalciferol products on the EU market or the products used in, as otherwise required by the Bioequivalence Guideline.

This is a well-established use application and no clinical and pharmacokinetic studies have been performed. The MAH has provided comparative data with three different cholecalciferol products from the Dutch, German, and UK markets containing different oil bases (medium chain triglycerides, maize oil, and peanut oil). The physicochemical qualities of the products were shown to be comparable, including: identification, average fill weight, average total weight, disintegration, assay of cholecalciferol, identification and assay of butylhydroxytoluene (BHT) and related substances. Appearance (including size of capsules) and loss on drying (of the gelatin shell) were not taken into account.

Manufacturing process

The manufacturing process has been adequately validated according to relevant European guidelines. The process consists of the preparation of the capsule fill material, the preparation of the gelatin mass, encapsulation, drying, inspection, and packaging. Process validation data on the product have been presented for one medium scale and two full scale batches of the fill material, divided over three batches per strength of the lower two strengths, and three medium scale batches of the fill material, divided over three batches per strength of the two higher strengths. Although the manufacturing process is considered a non-standard process due to the low cholecalciferol content, the provided process validation data are considered sufficient in view of the long-term (30 years) experience of the drug product manufacturer with manufacturing soft capsules.

Control of excipients

The excipients comply with the Ph. Eur. and USP (United States Pharmacopoeia) specifications. 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, identification of cholecalciferol, average fill weight, average total weight, disintegration, loss on drying, uniformity of dosage units (mass variation), assay of cholecalciferol, identification of BHT, assay of BHT, related substances, identification of colouring agents and microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A risk assessment on elemental impurities is presented to justify the absence for a test for (specific) heavy metals. A suitable risk evaluation on the formation of nitrosamine impurities has been provided.

Satisfactory validation data for the analytical methods have been provided. The forced degradation studies have confirmed the methods for assay and related substances as reliable measures for stability.

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

Stability of drug product

Stability data on the product have been provided on three production scaled batches per strength (for 25,000 IU strengths, one batch is included based on a bracketing approach) stored at 25°C/60% RH (24 months), 30°C/75% RH (24 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC-Al blister packs. Based on the provided real time stability data, the claimed shelf life of 24 months is justified. The available stability data do not indicate that there is a need to adopt a specific storage temperature. Based on photostability results, the capsules should be stored in the original packaging in order to protect from 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 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 Colecalciferol 1A Pharma 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

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods and available as a dietary supplement. It is also produced endogenously when UV light strikes the skin and triggers vitamin D synthesis. However, vitamin D obtained from sun exposure, food and supplements is biologically inert and must undergo two hydroxylations for activation.

Mode of action

Vitamin D is a fat-soluble vitamin that acts as a steroid hormone. The primary source of vitamin D is UVB induced conversion of 7-dehydrocholesterol to vitamin D in the skin. Vitamin D has a pivotal role as a calcaemic hormone, but vitamin D metabolites also have important non-calcaemic (non-classical) actions. The non-classical effects include actions on the cardiovascular system, regulation of innate and adaptive immune systems, a role in inflammatory and autoimmune diseases, release of insulin by pancreatic β cells and prevention of solid organ tumours. Vitamin D undergoes two hydroxylations in the body for activation. The first one occurs in the liver and converts vitamin D to 25(OH)D also known as calcifediol. The second hydroxylation occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D (1,25(OH)2D), also known as calcitriol. Calcitriol has a half-life of about 15 hours while calcifediol has a half-life of about 15 days. Vitamin D binds to vitamin D receptors (VDRs) throughout the body. Calcifediol (25(OH)D) is transformed by renal or extrarenal 1α-hydroxylase into the active 1,25(OH)2D which circulates at much lower serum concentrations than 25(OH)D but exerts a much higher affinity for the VDR. The enzyme of 1α-hydroxylase is also expressed in many other cell types including those of the vascular wall, and the conversion of 25(OH)D to the active 1,25(OH)2D happens at the level of the specific cell or tissue before being catabolised to the biologically inactive calcitroic acid. Moreover, there are many genes, modulated in part by vitamin D-encoding proteins, that regulate cell proliferation, differentiation, and apoptosis. The active form of vitamin D – 1,25(OH)2D – acts through its specific zinc-finger nuclear receptor (VDR) analogous to the ones for oestrogens and retinoic acid. It enters the target cells to exert paracrine or endocrine effects, binds to the nuclear receptor VDR and induces a conformational change of the VDR that promotes its interaction with the retinoid X receptor (RXR). The VDR/RXR complex induces transcriptional regulation of a variety of genes (Deluca, 2004; Nair and Maseeh, 2012; Christakos et al., 2015; Pilz et al., 2018).

Vitamin D promotes calcium absorption in the gut and maintains adequate serum levels of calcium and phosphate to ensure normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodelling by osteoblasts and osteoclasts. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D protects older individuals from osteoporosis. Serum concentration of 25(OH)D is used as the best indicator of vitamin D status. It reflects vitamin D produced in the skin and that obtained from food and/or supplements and has a long circulating half-life of 15 days. However, serum 25(OH)D levels do not indicate the amount of vitamin D stored in body tissues (Tolerable Upper intake levels for vitamins and minerals,

Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies, February 2006).

Vitamin D3 and autoimmune diseases in mice

The first experimental evidence of a link between vitamin D status and inflammatory bowel disease (IBD) comes from an animal model for IBD that was developed by Cantorna et al. (2000). Interleukin 10 (IL-10) knock-out mice that spontaneously develop symptoms resembling human IBD were made to be vitamin D deficient or were supplemented with active vitamin D. Treatment with 1,25(OH)2D3 treatment for as little as two weeks ameliorated IBD symptoms in these mice (Cantorna et al., 2000). A mouse model for the human disease of multiple sclerosis (MS) has been developed: the experimental autoimmune encephalomyelitis (EAE) model. 1,25-dihydroxycholecalciferol [1,25-(OH)2D3] has been shown to inhibit the progression of EAE in mice while vitamin D deficiency resulted in an increased susceptibility of mice to EAE (Cantorna et al., 1996).

Rheumatoid arthritis (RA) is another autoimmune disease that can be imitated with two different animal models: murine (mouse) Lyme arthritis and collagen-induced arthritis. Cantorna et al. (1996) also investigated the putative positive effects of vitamin D supplementation in mice that were infected with Borrelia burgdorferi (the causative agent of Lyme arthritis) or immunised with type II collagen. Supplementation with 1,25-(OH)2D3 minimised or prevented symptoms of arthritis in the treated group, while mice in the control group either developed severe arthritis or their symptoms worsened (Cantorna et al., 1996).

Vitamin D status and living environment in monkeys

In a recent small study in male Rhesus monkeys, Preston et al. (2018) showed that vitamin D status of those primates was highly depended upon sun exposure and dietary sources. The investigators assessed the vitamin D status in the blood of monkeys housed in high amounts of sunlight (corn-cribs), medium sunlight (corrals with shaded areas) and minimal sunlight (quarantine cages). 25(OH)D, which is the preferred metabolite to determine vitamin D status, was determined in the serum using High Performance Liquid Chromatography (HPLC). 25(OH)D levels in blood were significantly greater in corn-crib housed animals than in coral or quarantine-housed animals ($p > 0.01$ and $p > 0.001$ respectively). Significant differences of serum levels were not found when ages of animals housed in the same environment were compared. Those results emphasize the importance of the environment in which subjects typically spend their time when vitamin D results are interpreted (Preston et al., 2018).

Bone remodelling in hypervitaminosis D3 in rabbits

Normal bone growth and modelling is based on a balance between cartilaginous growth, maturation and resorption together with osteoblastic and osteoclastic activity. Both mechanisms require adequate blood supply. To investigate the mechanism of bone changes in vitamin D hypervitaminosis, experiments were designed in rabbits exposed to different doses of vitamin D, and radiographs were analysed at early stages and 6 to 12 weeks after vitamin D withdrawal. The rabbits of the control groups and those that received a small dose of vitamin D3 (60,000 IU per week for 1,2 and 3 weeks) showed no change in radiography, microangiography or pathology. However, rabbits that received medium (300,000 IU per dose for 3 doses with a 2-week interval between doses) or large doses of vitamin D3

(3,000,000,000 IU/kg/dose, 6 doses with 1-week interval between doses), showed morphologic changes with those being less severe in the medium dose group. Radiograms of the long bones and ribs showed subperiosteal resorption, linear intracortical lucencies and periosteal new bone formation. The vascular ingrowth and the resorption of the calcified chondromatrix were abnormal. The metaphyseal and physeal (growth plate) changes were attributed to reinvasion of vessels between the calcified chondromatrix and physeal or articular cartilage, with recovery of normal endochondral ossification (Jiang et al., 1991).

## III.2 Pharmacokinetics

Intestinal absorption and body retention of vitamin D was evaluated by Lorentzon and Danielson in 1985. Tritiated cholecalciferol ([3H]-D3) was intragastrically administered to rats previously fed with different amounts of vitamin D. It was found that animals with vitamin D deficiency accumulated high levels of serum radioactivity while they excreted less radioactivity in their 3-day feces compared to animals without vitamin D deficiency (Lorentzon and Danielson, 1985).

A study of Bikhazi and Hasbini investigated the brush-border mechanistic passage of vitamin D and 1,25(OH)2D metabolite. Radiolabelled cholecalciferol and 1,25(OH)2D were measured in intestinal perfusates and portal blood samples of rats injected with an inhibitor of protein and chylomicron synthesis. The amount of radiolabelled vitamin D lost from the perfusate was similar for the experimental and the control group of rats. However, treated rats showed a drastic increase in radiolabelled D3 retention in the intestine and a reduction in the portal plasma fraction (Silva and Furlanetto, 2018).

More recent *in vitro* studies with a cell model (CaCo2 cells) showed that long fatty acid chains that modulate cholesterol absorption also interfere with vitamin D absorption and that, in mice, vitamin D bioavailability was 15 times lower in mice in the presence of a phytosterol that is known to reduce dietary cholesterol absorption (Goncalves et al., 2013; Silva and Furlanetto, 2018). From animal studies, *in vitro* studies and clinical studies in different groups of individuals, vitamin D bioavailability seems to be improved when vitamin D is given with fat containing food and is impaired by intestinal fat malabsorption (Silva and Furlanetto, 2018).

A pre-clinical investigation aimed to obtain single dose pharmacokinetics in dogs from two different oral cholecalciferol formulations, using corrective measures to overcome the interference of endogenous cholecalciferol. Thus, Patel et al. (2017) developed a fit for purpose method to ensure accurate and precise measurement of cholecalciferol to support the planned pharmacokinetic study comparing the two formulations of cholecalciferol in dogs. Even though numerous assays have been published that involve LC-MS/MS for the quantification of cholecalciferol in serum/plasma it is not easy to establish a method that would completely remove endogenous cholecalciferol and use a vitamin D3 free serum environment for the comparative pharmacokinetic studies of two cholecalciferol formulations. In this preclinical study, six dogs were fasted overnight and received 60,000 IU of cholecalciferol of reference and test product by mouth. Blood samples were collected on day 0 (baseline establishment) and after dosing on day 1 up to 28 days. The serum samples

were extracted using protein precipitation/solid phase extraction and analysed to determine cholecalciferol by LC-MS/MS assay with calibrators prepared from cholecalciferol free serum. Standard pharmacokinetic analysis was carried out to assess pharmacokinetic parameters. Interestingly, serum cholecalciferol concentration vs. time profiles for the two formulations was almost superimposable. None of the PK parameters showed statistically significant differences ($p > 0.05$) between the two treatments. Pharmacokinetics of cholecalciferol was comparable between reference vs. test formulations. The procedures, baseline correction and employment of cholecalciferol devoid serum, can be readily adopted in future pharmacokinetic studies in animals or humans (Patel et al., 2017).

## III.3 Toxicology

Single- and repeated-dose toxicity

Toxic effects of vitamin D are related primarily to the role of free 1,25(OH)2D in plasma calcium regulation. Excessive production of the active vitamin D metabolite or greatly increased plasma 25(OH)2D may result in elevated plasma calcium levels due to overstimulated intestinal absorption and excessive calcium mobilization from bone. Hypercalcemia may also lead to an increased calcium excretion from the urine (hypercalciuria) (Vieth, 1990; Pettifor et al., 1995; Tolerable Upper intake levels for vitamins and minerals, Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies, February 2006; Reichel et al., 1989). Hypercalcemia is defined as a serum calcium above 2.75 mmol/L or ionised calcium above 1.35 mmol/L. Hypercalcemia associated with hypervitaminosis leads to numerous debilitating effects (including loss of tubular concentration function of the kidney, reduced glomerular filtration rate and calcification of soft tissues).

Several animal studies have been conducted involving systematic vitamin D intoxication over the past three decades in a variety of different species, including rats, cows, pigs, rabbits, dogs, and horses. As knowledge of vitamin D metabolism became more and more precise, focus of the research shifted to the levels of the metabolite 25(OH)D that must be exceeded to cause hypercalcemia. Shephard and DeLuca proceeded to acute intoxication of rats with graded oral doses of Vitamin D3 (Jones, 2008).

Genotoxicity

Vitamin D3 was tested in Salmonella typhimurium assay at doses 0.033 to 10 mg/plate in the presence of rat or hamster liver S9. Vitamin D3 was negative in this assay (Tolerable Upper intake levels for vitamins and minerals, Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies, February 2006).

Carcinogenicity

No information on potential carcinogenicity of vitamin D3 was discussed by the MAH. However, vitamin D is an endogenous substance produced naturally by contact of the skin by UV light, therefore any cancer potential risk from this replacement therapy is not expected to exceed that of a population with normal vitamin D level. In addition, vitamin D was shown to have direct anti-proliferative effects against a number of cancer cells *in vitro*, including colon, breast, prostate, and hematopoietic cells.

Reproductive and developmental toxicity

Vitamin D has been found to be teratogenic in animals when administered in doses 4-15 times the recommended human dose. Offspring from pregnant rabbits treated with high doses of vitamin D were presented with lesions reminiscent of those in cases of supravalvular aortic stenosis and others were presented with vasculo-toxicity similar to what adults experience upon acute vitamin D toxicity (Stockton and Paller, 1990; Tolerable Upper intake levels for vitamins and minerals, Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies, February 2006). Toda et al. (1985) showed that six week old piglets delivered from female pigs that received vitamin D3 highly enriched diets had more degenerated smooth muscle cells than those fed with low doses.

In a study of 2012, Ogamba et al. investigated the effect of cholecalciferol over dosage on pregnancy outcome in white albino mice. They used four groups of pregnant female albino mice. In three groups they administered high doses of vitamin D3 for a period of 22 days while the control group was only given saline and they studied parameters such as number of litters per delivery, average weight and length of the litters. The three experimental groups were treated with low dose 600 IU/kg, medium dose 1200 IU/kg or high dose 1800 IU/kg for 22 days. The number of litters was reduced only for the medium and the high dose treated group compared to the control group but there was significant reduction in the average weight and length of the litters of treated mice compared to the control ones. Overall, very high doses of vitamin D negatively affected pregnancy outcome in white albino mice, probably by inducing intrauterine growth retardation or down regulating the VDRs and inhibit fibroblast growth factor 23 synthesis (Ogamba et al., 2011).

Vitamin D deficiency is common in pregnant women and is increasingly recognised as a public health problem. It is increasingly recognised that vitamin D has anti-inflammatory effects (Krishnan and Feldman, 2011). A 2011 report demonstrates that vitamin D regulates placental inflammation (Liu et al., 2011). Nevertheless, whether vitamin D protects against LPS-induced adverse developmental outcomes remain to be determined. A 2013 study in mice investigated the effects of supplementation with vitamin D3 during pregnancy on lipopolysaccharide (LPS)-induced neural tube defects (NTDs). Pregnant mice except controls were intra-peritoneally injected with LPS (25 μg/kg) daily from gestational day 8 to 12. In the LPS(þVitD3) group, pregnant mice were orally administered with vitamin D3 (25 μg/kg) before LPS injection. As expected, a 5-day LPS injection resulted in 62.5% (10/16) of dams and 20.3% of foetuses with NTDs. An additional experiment showed that a 5-day LPS injection downregulated two major folate transporters in placentas. Consistent with downregulation of placental folate transporters, folate transport from maternal circulation into embryos was disturbed in LPS-treated mice. Interestingly, supplementation with vitamin D3 during pregnancy prevented LPS-induced NTDs through inhibiting placental inflammation and improving folate transport from maternal circulation into the embryos. Therefore, vitamin D3 may have a potential preventive utility for protecting against LPS-induced developmental toxicity (Chen et al., 2015).

Toxicity studies on excipients

Overall, the excipients used in the production of the end product are safe and generally regarded as non-toxic in the concentrations used. The MAH discussed literature on the

excipients, including butylhydroxytoluene (BHT), medium-chain triglycerides, gelatin, glycerol, titanium dioxide and iron oxide. Based on this information, it could be concluded that the excipients of the final formulation are not of toxicological concern.

### III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Colecalciferol 1A Pharma is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary. In addition, Cholecalciferol Sandoz contains Vitamin D3 as the active substance, which is a naturally occurring vitamin. Furthermore, the MAH calculated the Predicted Environmental Concentrations in surface water, which did not exceed the trigger value. Therefore, no further studies are required and vitamin D3 is considered not to pose a risk to the environment.

### 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 includes over 380 publications up to and including the year 2019 and justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

### IV.2 Pharmacokinetics

The MAH provided information on the pharmacokinetics of vitamin D, the use in special populations and potential interactions. Bridging to the literature was sufficiently supported.

Absorption, distribution and elimination

The absorption of vitamin D3 is a complex process containing both exogenous and endogenous sources of cholecalciferol and is controlled by a number of physiological processes and factors. These factors include variations in the physiochemical state of the vitamin D (molecular forms, potency and their physiological linkages), the complexity of food matrix (the amount and type of fatty acids, dietary fibres and presence/ absence of vitamin D enhancer and inhibitor), and the interaction of other fat soluble compounds with vitamin

D as well as the host-associated factors (age, disease, surgery, obesity, genetic variation etc.) (Maurya and Aggarwal 2017). Moreover, vitamin D absorption is not exclusively a simple diffusion process, as previously assumed, but rather a mechanism that involves membrane carriers (Silva and Furlanetto, 2017). In terms of formulation aspects, oily-based formulations are considered more effective than ethanol-based formulations (Maalouf et al., 2008) or dry composition solid forms such as tablets (Grossmann and Tangpricha, 2010). Moreover, the type of fatty acids (medium or long chain) and the degree of saturation in the vitamin D delivery medium have been also suggested to affect the bioavailability of vitamin D (Hollander et al., 1978, Holmberg et al., 1990, Niramitmahapanya et al., 2011, Maurya and Aggarwal, 2017). Cholecalciferol and its metabolites are excreted mainly in the bile and faeces. A small percentage of an administered dose is found in urine. The absorption, distribution, biotransformation and elimination of vitamin D and its metabolites were adequately discussed by the MAH.

Special populations

The literature supported that chronic renal failure is associated with a defect in the metabolism and excretion of vitamin D, therefore the SmPC describes a contraindication for use of the product in these patients.

In patients with hepatic impairment, hepatic conversion of vitamin D to 25(OH)D does not seem to be severely affected and thus no dosage adjustment is recommended. In a clinical study of 1982, the intestinal absorption and 25-hydroxylation of vitamin D in patients with primary biliary cirrhosis has been examined. The results showed that the absorption was severely impaired in test subjects but the hepatic conversion of vitamin D into 25-OH D was well preserved (Danielsson et al., 1982). Bikle et al (1984) studied and compared free 1,25(OH)2D levels in serum from normal subjects, pregnant subjects and subjects with liver disease.

In subjects with liver disease the mean total 1,25(OH)2D concentration and the mean vitamin D binding protein (DBP) concentration were nearly half normal values, whereas the mean free 1,25(OH)2D level was similar to normal values (Bikle et al., 1984). A number of reports have demonstrated that other than renal cells/tissues express also 1α-hydroxylase *in vitro* (Adams & Hewison 2012). In humans, these extrarenal sources of 1,25(OH)2D only contribute significantly to circulating 1,25(OH)2D levels during pregnancy and in pathological conditions such as sarcoidosis, tuberculosis, granulomatous disorders and rheumatoid arthritis (Harris & Dawson-Hughes, 2002, Holick et al., 2011).

Interactions

Concomitant use with large doses of calcium may increase the risk of hypercalcaemia. The use of digitalis and other cardiac glycosides combined with vitamin D may increase the risk of digitalis toxicity (arrhythmia). Systematic corticosteroids inhibit the absorption of calcium and therefore long-term use of corticosteroids may offset the effect of vitamin D. Other substances which were discussed by the MAH included ion exchange resins (e.g. cholestyramine), orlistat, magnesium, anticonvulsants, like phenytoin and barbiturates (e.g. primidone), calcitonin, etidronate, gallium nitrate, pamidronate or plicamycin, phosphor used in large doses, actinomycin and imidazole antifungal agents, rifampicin and isoniazid.

Bridging

Colecalciferol GAP was used to bridge Colecalciferol 1A Pharma to the literature. The MAH showed that the product Colecalciferol GAP is identical to Colecalciferol 1A Pharma. From the provided data, it may be expected that the pharmacokinetics, efficacy and safety are comparable, taking into account the comparison of the pharmaceutical form and ingredients of Colecalciferol 1A Pharma and those mentioned in literature. Moreover, Colecalciferol 1A Pharma does not contain critical excipients. Formulations described in literature include soft capsules with cholecalciferol in an oily solution. As Colecalciferol 1A Pharma is also a soft capsule with cholecalciferol in an oily solution, comparative dissolution data are considered not needed, as dissolution experiments will be hampered in an aqueous media, due to the formulation being an oily solution. From a clinical point of view, it was sufficiently shown that the intent of vitamin D supplementation is to increase the deposit of vitamin D3 on a long term basis, although regular vitamin D follow-up measurements of 25(OH)D levels are not recommended in all groups.

## IV.3 Pharmacodynamics

Vitamin D has been identified as one of the key nutrients that contributes to the development and maintenance of optimum bone mass. Three mechanisms are involved: it affects calcium and phosphate absorption in the intestine, calcium mobilization in bone and calcium reabsorption in the kidney. Part of the effects are dependent from parathyroid hormone. The MAH describes several studies that investigated the effect of different dosing regimens on serum 25(OH)D concentration in healthy subjects.

Regarding daily dosing regimens, one study concludes that in healthy 70 kg adults, an 8-week course of vitamin D3 at 10 micrograms/day (400 IU/day) would raise serum 25(OH)D by 9 nmol/l (Barger-Lux et al., 1998). Another study showed daily intake of 100 micrograms (4000 IU/day) safely increased 25(OH)D serum levels to high-normal values (Vieth et al., 2001). Regarding, a single dosing regime, a study showed that a single oral dose of 100,000 IU raises the serum 25(OH)D to 42.0 ng/mL (SI units: 105 nmol/l). The study states that the dosing interval of single doses should be ≤2 months to ensure continuous serum calcidiol concentrations above baseline (Ilahi et al., 2008). Furthermore, one study is reviewed that compared daily versus single administration. After 28 days, no difference in serum concentration was observed (Meekins et al., 2014).

These data support sufficiently that both daily administration and a single dose administration can adequately elevate serum 25(OH)D. The actual used dosage should be dependent on the baseline concentration.

## IV.4 Clinical efficacy

The MAH provided a large quantity of randomised controlled clinical trials and meta-analyses supporting the indications.

Treatment of vitamin D deficiency and initial treatment of vitamin D deficiency

The MAH has provided several randomised clinical trials that studied the effect of cholecalciferol suppletion on serum 25(OH)D levels in otherwise healthy patients with a baseline vitamin D <50 nmol/L. Doses varied from 800 IU daily to 50,000 IU once per 25 days. All studies showed increased levels of serum 25(OH)D after at least 3 months. Levels were in the normal range and did not exceed the level of vitamin D intoxication (i.e. not >200 nmol/L). (van Groningen et al., 2010; Gallagher et al., 2012; De Niet et al., 2018)

Prevention of vitamin D deficiency in adults with an identified risk

There are many causes of vitamin D deficiency, including reduced skin synthesis and absorption of vitamin D, inadequate alimentary intake or intestinal malabsorption. Vitamin D deficiency is also highly prevalent in nursing home patients and obese persons. Also, some medications are responsible for vitamin D deficiency (e.g. anticonvulsants, glucocorticoids and HAART). Therefore, these groups of patients are at risk to develop vitamin D deficiency. The literature provided by the MAH included a large quantity of clinical studies investigating the effect of cholecalciferol suppletion subjects at risk for vitamin D deficiency. The relevant studies had a variety of subjects: elderly nursing-home patients, postmenopausal women, dark-skinned persons, obese subjects, patients on relevant concomitant medications or those with malabsorption. In all studies there was a beneficial effect observed on the levels of serum 25(OH)D with the use of 800 IU up to 1200 IU cholecalciferol daily. (Lips et al., 1988; Himmelstein et al., 1990; Buckley et al., 1996; Recker et al., 2006; Ish-Shalom et al., 2008; Jorgensen et al., 2010; Karaplis et al., 2011; Wamberg et al., 2013; Ng et al., 2014).

Special populations

The MAH summarised 17 studies concerning special populations. These include patients with renal insufficiency, hepatic insufficiency, obese subjects and adolescents. The studies that were relevant did not show alterations in dose or outcome. Thus, no dose adjustments were deemed necessary for renal impairment, hepatic impairment, nor for adolescents. (Chandra et al., 2008; Oksa et al., 2008; Dong et al., 2010; Harel et al., 2011; Malham et al., 2012; Pappa et al., 2012). According to the SmPC cholecalciferol is not advised in patients with severe renal impairment, nor in children under the age of 12 years.

## IV.5 Clinical safety

The safety profile of cholecalciferol is well-known. In general, vitamin D is well tolerated. However, there is a risk for toxicity, especially with higher dosages, for which hypercalcaemia and hypercalciuria are the main adverse events. The MAH provided additional data from twelve clinical trials regarding safety information. These studies used different dosing regimens: daily doses of 800 IU to 4000 IU per day and weekly doses of 20,000 IU to 50,000 IU per week. Safety parameters included 25(OH)D within normal range and not exceeding toxicity levels (> 100 ng/mL), as well as serum calcium concentration, parathyroid hormone, bone alkaline phosphatase and urinary calcium levels. No adverse events were reported in these studies. (Lips et al., 1988; Himmelstein et al., 1990; Honkanen et al., 1990; Aloia et al., 2005; Hathcock et al., 2007; Kennel et al., 2010; Binkley et al., 2011; Zabihiyeganeh et al., 2013; Jetty et al., 2016; Takacs et al., 2017; Toth et al., 2017).

The MAH provided data on serious adverse events and deaths. No serious adverse events occurred often enough to be labelled common or very common. Most adverse events are reported in gastrointestinal disorders, skin and subcutaneous disorders and metabolism and nutrition disorders. Hypercalcaemia is reported as uncommon, however, theoretically this may lead to death. Accordingly, a warning about hypercalcaemia is provided in the SmPC. (Carroll & Schade 2003; Reese 2006; Zittermann et al., 2013, Gupta et al., 2014; van den Ouweland et al., 2014; Malangone & Campen 2015; Tebben et al., 2016, Marcinowska-Suchowierska et al., 2018; Martindale 2019).

Cholecalciferol has been studied both in elderly patients (800 IU per day) and in school children (14,000 IU per week). No safety concerns have risen. However, according to the SmPC and in absence of sufficient literature, vitamin D should not be used in children under the age of 12 years. (Lips et al., 1988; Himmelstein et al., 1990; Honkanen et al., 1990; Maalouf et al., 2008).

Additionally, for patients with concomitant sarcoidosis, toxicity has been reported during vitamin D treatment. (Sharma, 1996; Tebben et al., 2016) This is represented as a warning in the SmPC. Hypersensitivity reactions to cholecalciferol or its active metabolite calcitriol are rare. Two reported cases of suspected hypersensitivity have been reported (Amandeep et al., 1999, Unal et al., 2016).

In conclusion, the clinical safety of vitamin D was sufficiently discussed with supporting literature.

## 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 Colecalciferol 1A Pharma.

**Table 1. Summary 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 and preventing a vitamin D deficiency is well known. The bibliographic data showed vitamin D deficiency was resolved, improved, or prevented as indicated. The MAH discussed several studies to support the efficacy and safety of vitamin D in the treatment and prevention of vitamin D deficiencies in the indicated populations. No

new clinical studies were conducted. The proposed indications are widely used and known and sufficiently discussed in the provided literature and therefore acceptable.

# 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 Rabeprazole GAP, gastroresistant tablets, 10mg / 20mg (PT/H/881/001-002/DC) for the layout and design, and to Benferol 25,000 IU, 50,000 IU and 100,000 IU Soft capsules (DK/H/2491/001-003/DC) for the content. 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

Colecalciferol 1A Pharma 800 IU, 3200 IU, 25,000 IU, and 50,000 IU, soft capsules have a proven chemical-pharmaceutical quality. The products have an adequate efficacy and safety profile and are 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 31 August 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 |