COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vitamin D Will 25000 IE and 50000 IE soft capsules

(cholecalciferol)

NL/H/4946/001-002/DC

Date: 9 October 2020

This module reflects the scientific discussion for the approval of Vitamin D Will . The procedure was finalised on 15 June 2020. 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	D-binding Protein
EAE	Experimental Autoimmune Encephalomyelitis
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 Defects
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vitamin D Will 25000 IE and 50000 IE soft capsules from Will Pharma Benelux.

The product is indicated for:

- Treatment of vitamin D deficiency.
- Prevention of vitamin D deficiency in high-risk patients.
- As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.

This medicine is indicated in adults.

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

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of cholecalciferol. 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. The MAH also submitted data showing that the composition of Vitamin D Will is similar to the composition of other products that have been widely used world-wide for the same indications.

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Vitamin D Will 25000 IE is a white opaque, size 3, oval soft capsule. Each capsule contains 25,000 IU cholecalciferol (equivalent to 0.625 mg vitamin D3).
Vitamin D Will 50000 IE is a red opaque, size 6, oval soft capsule. Each capsule contains 50,000 IU cholecalciferol (equivalent to 1.25 mg vitamin D3).

The soft capsules are packed in white opaque PVC/PVDC/Aluminium blisters.

The excipients are:
Capsule fill – butylhydroxytoluene (BHT), medium chain triglyceride oil
Capsule shell – gelatine (E441), glycerol (E422), titanium dioxide (E-171), iron oxide red (E-172) (50000IU only), water purified

The two strengths are dose proportional.

II.2 Drug Substance

The active substance is cholecalciferol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white crystalline powder and it is practically insoluble in water, freely soluble in ethanol (96 per cent), and soluble in trimethylpentane and in fatty oils. Issues in regards to polymorphism are not relevant, as cholecalciferol is present in solution in the final 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 in line with Ph. Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. The supplementary test for residual solvent methyl formate stated on the CEP is adopted by the MAH. In addition, the microbiological quality of the active substance is controlled in accordance with Ph. Eur. 5.1.4. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four batches.

Stability of drug substance
Assessment of the stability data was not part of the CEP application, i.e. no re-test period is stated on the CEP. Stability data on the active substance have been provided for 3 batches stored at 2-8°C (long-term conditions) for 60 months and at 25°C/60% RH (accelerated conditions) for 6 months. The active substance is stable for 60 months if stored at a temperature between 2°C and 8°C, when stored in the proposed packaging.

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 pharmaceutical development of the product has been adequately performed.
As the active substance is already dissolved, there is no reason to perform dissolution testing on the finished product. Thus 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.

Manufacturing process

First, the fill material preparation is performed. Secondly, the gel mass is prepared. Thirdly, the encapsulation procedure is followed. The capsules are then dried, inspected, polished and finally packed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches.

Control of excipients

Reference to Ph. Eur. and USP is made for the excipients. These specifications are acceptable.

Quality control of drug product

The product release and shelf-life specification includes tests for appearance, identification cholecalciferol, average fill weight, average total weight, disintegration, loss on drying, uniformity of dosage units (mass variation), assay cholecalciferol, identification of BHT, assay of BHT, related substances, identification of colouring agents, microbiological examination.
The finished product specification is acceptable. A risk assessment on elemental impurities is presented to justify the absence for a test for (specific) heavy metals. A risk evaluation on the formation of nitrosamine impurities has been provided and is acceptable. A confirmation of no risk of nitrosamine presence identified is provided. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three batches per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three production-scale batches of the 50,000 IU strength and on one batch of the 25,000 IU strength (based on a bracketing approach) stored at 25°C/60% RH (18 -24 months), 30°C/75% RH (18 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 pack.
There are no clear changes or trends observed at any of the storage conditions. Extrapolation of the stability data is acceptable and therefore the shelf-life of 24 months is

acceptable. The available stability data currently 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 package in order to protect from light.

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

Animal tissue (sheep wool) is used in the manufacture of cholecalciferol. The active substance meets the criteria described in the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies of the European Pharmacopoeia'. The excipients which potentially may originate form an animal source are gelatine and glycerol. A CEP on TSE safety for gelatine is presented. A statement from the manufacturer of glycerol indicates that glycerol does not originate from an animal source.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vitamin D Will 25000 IE and 50000 IE soft capsules have 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

Mode of action

Vitamin D is a fat-soluble vitamin that acts as a steroid hormone. 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 calcemic hormone, but it is now clear that vitamin D metabolites have also important non-calcemic (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 tumors. 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 one 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 h while calcifediol (25(OH)D) has a half-life of about 15 days. Vitamin D binds to vitamin D receptors (VDRs) throughout the body. 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 catabolized 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 estrogens 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 (Pilz et al., 2018; Nair and Maseeh, 2012; Christakos et al., 2015; Deluca, 2004).
Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate to ensure normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling 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 store 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 – 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. 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. Interestingly, treatment with 1,25(OH)2D3 for as little as 2 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 so-called 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 Lyme arthritis and collagen – induced arthritis. Cantorna et al. 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 immunized with type II collagen. Supplementation with 1,25-(OH)2D3 minimized 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 – monkeys

In a recent small study in male Rhesus monkeys, Preston et al. 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 Vitamin D which is the preferred metabolite to determine Vitamin

D status, was determined in the serum using High Performance Liquid Chromatography (HPLC). 25 OH Vitamin 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 typically subjects spend their time when Vitamin D results are interpreted (Preston et al., 2018).

Bone Remodeling in Hypervitaminosis D3 - Rabbits

Normal bone growth and modeling 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 changes are 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 back in 1985. Tritiated Cholecalciferol ([3H]-D3) was intra-gastrically administered to rats previously fed with different amounts of vitamin D. From their results, 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).

Another 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 CaCo2 cells showed that long fatty acid chains that modulate cholesterol absorption also interfere with vitamin D absorption and that in mice cholecalciferol 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 very recent pre-clinical investigation aimed to obtain single dose pharmacokinetics in dogs from 2 different oral cholecalciferol formulations using corrective measures to overcome the interference of endogenous cholecalciferol. Thus, Patel et al. developed a fit for purpose method to ensure accurate and precise measurement of cholecalciferol to support the planned pharmacokinetic study comparing the 2 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 2 cholecalciferol formulations. In this preclinical study 6 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 2 formulations were almost superimposable. None of the pharmacokinetic parameters showed statistically significant differences ($p > 0.05$) between the 2 treatments. For example: C_{max} (ng/mL) and AUC_{inf} (ng·h/mL) derived after the baseline corrections were 708.65 and 38,877.18 for reference and 743.71 and 40,665.51 for test, respectively. Pharmacokinetics of cholecalciferol were comparable between reference and 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

III.3.1 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 over stimulated 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 ionized calcium above 1.35 mmol/L. Hypercalcemia associated with hypervitaminosis leads to numerous debilitating effects such as loss of tubular concentration function of the kidney, reduced glomerular filtration rate, calcification of soft tissues etc.

Several animal studies have been conducted involving systematic vitamin D intoxication over the past 3 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).

III.3.2 Genotoxicity

Vitamin D3 was tested in Salmonella typhimurium assay at doses 0.033 to 10 mg/plate (strains TA1535, TA1537, TA97, TA98, TA100 were used) 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).

Vitamin D3 was described as negative in the Ames test by the EFSA Scientific Committee on Food Scientific Panel on Dietetic Products. This was based on a manuscript by Mortelmans (1986).

III.3.3 Carcinogenicity

No information on potential carcinogenicity of vitamin D3 was discussed by the MAH. The MAH did not conduct any carcinogenicity studies based on information retrieved in the literature and on the FDA conclusions on vitamin D3 containing medicines. It is also worth mentioning that vitamin D is an endogenous substance produced naturally by contact of the skin by UV light, therefore any potential cancer risk from this replacement therapy is not expected to exceed that of a population with normal vitamin D level.
Furthermore, according to the World Health Organisation, 1,25-dihydroxyvitamin D3 (calcitriol) may act as a chemo-preventive agent against several malignancies including cancers of the prostate and colon. The mechanisms behind the chemo-preventive protection of vitamin D are up-regulation of adherence and signalling between epithelial cells, contact inhibition of proliferation and differentiation, cell cycle stabilization, promotion of apoptosis and anti-neo-angiogenesis.
Vitamin D has direct anti-proliferative effects against many cancer cells *in vitro*, including colon, breast, prostate and hematopoietic cells. Vitamin D reduces crypt cell proliferation in colonic tissue removed from individuals with familial adenoma polyposis.

III.3.4 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 vasculotoxicity like the one that 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. also showed that 6-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 (Toda et al., 1985-b).
In a more recent study of 2012, Ogamba et al. investigated the effect of cholecalciferol over dosage on pregnancy outcome in white albino mice. They used 4 groups of pregnant female albino mice. In 3 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 3 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 (FGF-23) synthesis (Ogamba et al., 2011). Vitamin D deficiency is common in pregnant women and is increasingly recognized as a public health problem. It is increasingly recognized 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 remains 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 ip injected with LPS (25 µg/kg) daily from gestational day (GD)8 to GD12. In LPSþVitD3 group, pregnant mice were orally administered VitD3 (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 placental proton-coupled folate transporter and reduced folate carrier 1, 2 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).

III.3.5 Studies on impurities

No studies on impurities were performed or provided.

III.3.6 Other Toxicity Studies

Excipients

Butyl hydroxytoluene (BHT) is used as an antioxidant in cosmetics, foods and pharmaceuticals. It is mainly used to delay or prevent the oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins. Butyl hydroxytoluene is also used at 0.5–1.0% w/w concentration in natural or synthetic rubber to provide enhanced colour stability. BHT has some antiviral activity and has been used therapeutically to treat herpes simplex labialis. It is readily absorbed from the gastrointestinal tract and is metabolized and excreted in the urine mainly as glucuronide conjugates of oxidation products. Although there have been some isolated reports of adverse skin reactions, butylated hydroxytoluene is generally regarded as non-irritant and non-sensitizing at the levels employed as an antioxidant. The toxic effects of BHT are most commonly encountered in laboratory animals after chronic administration and refer to lesions in hepatic cells. Ingestion of 4 g of BHT, although causing severe nausea and vomiting, has been reported to be nonfatal (Rowe et al., 2009, 6th edition). Based on the various studies taken into consideration, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) defined an admissible daily intake (ADI) of 0-0.3 mg/kg body weight/day, which means 18 mg/day (Pifferi et al., 2003; JEFCA, Joint FAO/WHO Expert Committee on Food Additives, 51st Technical Report Series).

Medium-chain triglycerides have been used in a variety of pharmaceutical formulations including oral, parenteral and topical preparations. In oral formulations, medium-chain triglycerides are used as the base for the preparation of oral emulsions, microemulsions, self-emulsifying systems, solutions, or suspensions of drugs that are unstable or insoluble in aqueous media, e.g. calciferol. Medium-chain triglycerides have also been investigated as intestinal absorption enhancers and have additionally been used as a filler in capsules and sugar-coated tablets, and as a lubricant or antiadhesion agent in tablets (Rowe et al., 2009, 6th edition).

Medium-chain triglycerides are generally regarded as essentially non-toxic and non-irritant materials. In acute toxicology studies in animals and humans, no irritant or other adverse reactions have been observed; for example, when they were patch-tested on more than 100 individuals, no irritation was produced on either healthy or eczematous skin. Medium-chain triglycerides are not irritating to the eyes. Similarly, chronic toxicology studies in animals have shown no harmful adverse effects associated with medium-chain triglycerides following inhalation or intraperitoneal, oral and parenteral administration. In humans, administration of 0.5 g/kg body-weight medium-chain triglycerides to healthy individuals produced no change in blood or serum triglycerides compared to subjects receiving the same dose of the long-chain triglyceride triolein. In patients consuming diets based on medium-chain triglycerides, adverse effects reported include abdominal pain and diarrhea. Medium-chain triglycerides are listed as generally recognized as safe (GRAS) and included in the FDA Inactive Ingredients Database (topical preparations). It is included in non-parenteral and parenteral medicines licensed in Europe, and included in the Canadian List of Acceptable Non-medicinal Ingredients (Rowe et al., 2009, 6th edition).

Gelatine is most frequently used to form either hard or soft gelatine capsules. Gelatine capsules are unit-dosage forms designed mainly for oral administration. Soft capsules are mainly filled with semi-solid or liquid fillings.
Gelatine is soluble in warm water (>30^{o}C), and a gelatine capsule will initially swell and finally dissolve in gastric fluid to release its contents rapidly. The gelatine used to form the soft shells has a lower gel strength than that used for hard capsules, and the viscosity of the solutions is also lower, which results in more flexible shells. Additives to soft shell formulations are plasticizers here-in (glycerol 99.5%). Colouring and opacifying agents are also added. The filling can interact with the gelatine and the plasticizer chemically. There may be migration of filling components into the shell and plasticizer from the shell into the filler. These interactions must be considered during the formulation of the gelatine shell and the filling. In general, when used in oral formulations gelatine may be regarded as a non-toxic and non-irritant material. However, there have been rare reports of gelatine capsules adhering to the esophageal lining, which may cause local irritation. Hypersensitivity reactions, including serious anaphylactoid reactions, have been reported following the use of gelatine in parenteral products (Rowe et al., 2009, 6th edition). Gelatine is GRAS listed and included in the FDA Inactive Ingredients Database (dental preparations; inhalations; injections; oral capsules, pastilles, solutions, syrups and tablets; topical and vaginal preparations). It is also included in medicines licensed in the UK, Europe and Japan and in the Canadian List of Acceptable Non-medicinal Ingredients (Rowe et al., 2009, 6th edition).

Titanium dioxide is widely used in foods and oral and topical pharmaceutical formulations. It is generally regarded as an essentially non-irritant and non-toxic excipient. It is widely used in confectionery, cosmetics and foods, in the plastics industry, and in topical and oral pharmaceutical formulations as a white pigment. It is accepted as a food additive in Europe and included in the FDA Inactive Ingredients Database (dental paste; intrauterine suppositories; ophthalmic preparations; oral capsules, suspensions, tablets; topical and transdermal preparations), included in non-parenteral medicines licensed in the UK, and included in the Canadian List of Acceptable non-medicinal Ingredients (Rowe et al., 2009, 6th edition).

Iron oxides are widely used in cosmetics, foods and topical pharmaceutical applications as colorants and UV absorbers. However, iron oxides also have restrictions in some countries on the quantities that may be consumed, and technically their use is restricted because of their limited colour range and their abrasiveness. They are generally regarded as non-toxic and non-irritant excipients. The use of iron oxide colorants is limited in some countries, such as the USA, to a maximum ingestion of 5 mg of elemental iron per day. Iron oxides are accepted for use as a food additive in Europe and they are included in non-parenteral medicines licensed in many countries including Japan, UK and USA (Rowe et al., 2009, 6th edition).

Overall, the excipients used in the production of Vitamin D Will 25000 IU and 50000 IU soft capsules, are safe and generally regarded as non-toxic in the concentrations used.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Cholecalciferol WIL Pharma is intended for substitution of comparable products currently on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.
In addition, Cholecalciferol WIL Pharma contains Vitamin D3 as active substance, which is a naturally occurring vitamin. Furthermore, the MAH calculated the $PEC_{surfacewater}$, 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

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 pharmacodynamic, pharmacokinetic and toxicological properties of the active substance cholecalciferol are well known. The MAH has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics/pharmacodynamics

Vitamin D can be obtained from the diet and by the action of sunlight on the skin. The two forms of the vitamin that are best known and which are of nutritional significance are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Only some selected food contains significant amounts of vitamin D2 and D3. Vitamin D is absorbed in the small intestine, a process that requires the presence of fat, bile (mainly deoxycholic acid) and pancreatic enzymes, and is transported via lymph incorporated in chylomicrons, to the liver.

However, in normal circumstances most of the Vitamin D3 is produced in the skin by an ultraviolet light-induced photolytic conversion of 7-dehydrocholesterol to previtamin D3 followed by thermal isomerisation to vitamin D3. The active form of vitamin D3 is 1,25–dihydroxyvitamin D3 (1,25-(OH)2D3) and is formed following sequential hydroxylations in the liver and kidney, a process which is promoted by parathyroid hormone (PTH). Vitamin D and its hydroxylated metabolites 25(OH)D, 24,25(OH)2D, and 1,25(OH)2D are lipophilic molecules.

Because of their low solubility in the aqueous medium of plasma, vitamin D compounds are transported in the circulation bound to plasma proteins. The most important of these carrier proteins is the vitamin D-binding protein (DBP). Under normal physiological conditions, nearly all circulating vitamin D compounds are protein bound, which has a great influence on vitamin D pharmacokinetics. DBP-bound vitamin D metabolites have limited access to target cells and are, therefore, less susceptible to hepatic metabolism and subsequent biliary

excretion, which prolongs their half-life in circulation. Albumin and lipoproteins are also important plasma carrier proteins with lower affinities for vitamin D metabolites than DBP.

The final cleavage product of 1,25(OH)2D3, calcitroic acid, is biologically inert. Other polar metabolites of cholecalciferol have also been isolated, including 25,26 dihydroxy-cholecalciferol. A further metabolite may be produced in the kidney by 24-hydroxylation of 1,25(OH)2D3 to form 1,24,25(OH)3D3. There is also an enterohepatic recirculation of vitamin D and its metabolites, largely conjugated as glucuronides before secretion into the bile, and bile fistulae may thus lead to vitamin D depletion. Because of their high lipid solubility, cholecalciferol and its metabolites are eliminated slowly from the body. Cholecalciferol has a plasma half-life of 19 to 25 hours and a terminal half-life (the time needed for the amount of a compound present in all body stores to decrease by half) of weeks to months. Metabolites are eliminated primarily (96%) through the bile and faeces. Skeletal muscle and adipose tissue may provide a large storage reservoir from which vitamin D may be slowly released as plasma levels fall. In cross-sectional studies, especially those performed in populations living at relatively elevated latitudes in North America, Europe, and Asia, serum levels of the 25OHD metabolite are maximal some 30–60 d after peak sunlight exposure in the summer months.

Considering the pharmacological properties of cholecaliferol, particularly the extremely long body half-life of ~2 months, minor differences in absorption that may due to slightly different formulations (excipients of tablets, dissolution profile, formulation), are unlikely to have impact on the therapeutic goal, e.g. to achieve the vitamin D status as reflected by serum 25(OH)D concentrations.

IV.2 Bridging data of the products in the application with the products referred to in the literature

Recent literature reviews by Silva and Furlanetto (2018) and Borel et al. (2015) provide ample data on the bioavailability of vitamin D3 in humans. High dose vitamin D3 formulations, such as the Will Pharma 25,000 and 50,000 IU products, have been investigated in various clinical settings. No critical issues regarding the uptake and therapeutic effect (readout 25(OH)D blood levels) in the 25,000/50,000 IU range have been reported in healthy individuals. Vitamin D3 uptake was linearly dose-dependent (based on 25(OH)D blood levels). Formulation/matrix effects were investigated and no differences in bioavailability of vitamin D3 were reported. That means that the literature findings on bioavailability apply to the Will Pharma products.
Examples of comparable products on the market in the EU are: Solicol 50000 tablets, InvitaD3 50000 oral oil-based solution, Thorens 25000 oral oil-based solution and Colecalciferol Benferol 25,000 and 50,000 IU vitamin D3 soft gelatin capsules.
Colecalciferol Benferol 25,000 and 50,000 soft gelatine capsules (NL licence RVG 117092, 117094) are approved in the Netherlands, Luxemburg, Denmark, Norway, Sweden, Finland and Spain. The Will Pharma products and Colecalciferol Benferol 25,000 and 50,000 are equal in terms of bioactive and major capsule building materials. There are minor

differences in the selection of low-concentration excipients; this will not cause differences between these products in clinical outcome, both in terms of efficacy and safety.

IV.3 Clinical efficacy

The MAH submitted several studies to support the proposed indications and posology of 25,000 & 50,000 IU cholecalciferol. These studies used a variety of dosing schedules to achieve normal 25(OH)D levels after a certain period of treatment including loading doses and/or several weeks or months of treatment. The MAH combined abstracts of several articles. Most articles studied the effect of weekly or monthly dosing regimens, which revealed effective results on serum 25(OH)D. In the SmPC a cumulative loading dose of 100,000 IU over 1 week is recommended which is acceptable. This is also in alignment with the SmPC of Colecalciferol Benferol which states that vitamin D deficiency can be treated with a loading dose of 100,000 IU or an equivalent of four times 25,000 IU or twice 50,000 IU in one week.
The applicant proposed a dose of 25,000 IU/month – 25,000 IU/2 months for vitamin D insufficiency (serum levels 25-50 nmol/l or 10-20 ng/ml), long term maintenance therapy following treatment of deficiency in adults and the elderly, and prevention of vitamin D deficiency in high-risk patients which is acceptable and in alignment with other registered SmPCs.

Osteoporosis: As an adjunct to specific therapy for osteoporosis the applicant proposed 1 capsule of 25,000 IU once a month which is acceptable and equivalent to the already approved SmPCs.

IV.4 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. Hypercalcemia and hypercalciuria are the main adverse events. Monthly vitamin D doses in adults are approved in some registered EU procedures. Any specific discussion on the safety in high monthly dose is limited.

IV.5 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 D Will 25000 IE and 50000 IE soft capsules.

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.6 Discussion on the clinical aspects

Pharmacokinetics
The pharmacokinetics are adequately summarised by the MAH. In the two clinical addenda a rationale was provided why the statements regarding the pharmacokinetics of cholecalciferol can be bridged to the proposed formulation. The MAH did not submit a comparison of bioequivalence/PK data of Vitamin D Will and Vitamin D3 products already on the market, however these data were part of the articles/reviews discussed in the provided addenda.
It was sufficiently shown that all Vitamin D products described in the submitted literature have similar PK/PD characteristics with respect to the exposure to the main 25(OH) metabolite and no significant differences in efficacy.
Studies with different marketed products with significant different qualitative composition show no significant differences in exposure to the main 25(OH) metabolite. Therefore it may be concluded that the composition has no effect on the efficacy considering the PK/PD relationship of Vitamin D3.
Therefore, it can be concluded that Vitamin D Will is similar to the products described in the literature on which this well-established use application is based.

Efficacy/safety
Benefits
The clinical benefit of treating and preventing vitamin D deficiency is well known, as well as the clinical benefit of adjunct to specific therapy for osteoporosis. The bibliographic data submitted 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 and prevention of vitamin D deficiency. The studies provided in the clinical overview used a variety of dosing schedules to achieve normal 25(OH)D levels after a certain period of treatment including loading doses and/or several weeks or months of treatment.
In the SmPC a cumulative loading dose of 100,000 IU over 1 week is recommended which is acceptable. This is also in alignment with the SmPC of Colecalciferol Benferol (NL Licence RVG 117092, 117094) which states that vitamin D deficiency can be treated with a loading dose of 100,000 IU or an equivalent of four times 25,000 IU or twice 50,000 IU in one week.

As an adjunct to specific therapy for osteoporosis the MAH proposed 1 capsule of 25,000 IU once a month which is acceptable and equivalent to the already approved SmPCs.

Risks
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. Hypercalcemia and hypercalciuria are the main adverse events.

Benefit/risk balance

The MAH summarized multiple abstracts of articles. These studies report change in 25(OH) levels, with different strategies and revealed comparable results in different study populations. The proposed indications are acceptable and in alignment with other registered SmPCs of vitamin D products. Risk management is adequately addressed.
Overall, the benefit/risk assessment of Vitamin D Will is considered positive.

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 Colecalciferol 20,000 IU soft capsules (UK licence number: PL 20491/0001). Bridging is acceptable since the main efficacy and safety information is similar or identical. For bridging of the PL layout, reference is made to a Rebaprazole product. Rebaprazole is not considered the same class of medicinal product, but reference is acceptable for bridging of the layout only. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vitamin D Will 25000 IE and 50000 IE soft capsules have a proven chemical-pharmaceutical quality. Vitamin D Will is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

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 Colecalciferol Will Pharma, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 June 2020.

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

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