COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cholecalciferol INVOS 800 IU, 1000 IU, 3200 IU, 20000 IU and 25000 IU soft capsules

(cholecalciferol)

NL/H/4811/001-005/DC

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This module reflects the scientific discussion for the approval of Cholecalciferol INVOS 800 IU, 1000 IU, 3200 IU, 20000 IU and 25000 IU soft capsules. The procedure was finalised at 5 August 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	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
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cholecalciferol INVOS 800 IU, 1000 IU, 3200 IU, 20000 IU and 25000 IU soft capsules, from GAP S.A.

Cholecalciferol INVOS 800 IU and 1000 IU soft capsules are indicated for:

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

Cholecalciferol INVOS 3200 IU soft capsules is indicated for:

- Treatment of vitamin D deficiency in adults and adolescents.

Cholecalciferol INVOS 20000 IU and 25000 IU soft capsules are indicated for:

- Initial treatment of clinically relevant vitamin D deficiency 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 MAH 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 Cholecalciferol INVOS is similar to the composition of other products that have been widely used world-wide for the same indications.

Cholecalciferol has been widely marketed and used in the proposed indications for more than 10 years. Cholecalciferol is a well-established active substance in a variety of different pharmaceutical presentations.

The concerned member states (CMS) involved in this procedure were Austria, Greece, Germany, Spain, Portugal and Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

- Cholecalciferol INVOS 800 IU is a light-yellow opaque, oval soft capsule. Each capsule contains 800 IU cholecalciferol (equivalent to 20 micrograms vitamin D3).
- Cholecalciferol INVOS 1000 IU is an orange opaque, oval soft capsule. Each capsule contains 1000 IU cholecalciferol (equivalent to 25 micrograms vitamin D3).
- Cholecalciferol INVOS 3200 IU is a yellow opaque, oval soft capsule. Each capsule contains 3200 IU cholecalciferol (equivalent to 80 micrograms vitamin D3).
- Cholecalciferol INVOS 20000 IU is a pink opaque, oval soft capsule. Each capsule contains 20000 IU cholecalciferol (equivalent to 500 micrograms vitamin D3).
- Cholecalciferol INVOS 25000 IU is a white opaque, oval soft capsule. Each capsule contains 25000 IU cholecalciferol (equivalent to 625 micrograms vitamin D3).

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

The excipients are:
Capsule content – butylhydroxytoluene and medium chain triglyceride oil
Capsule shell – gelatin, glycerol, titanium dioxide (E171), yellow iron oxide (E172; 800 IU, 1000 IU and 3200 IU only), red iron oxide (E172; 1000 IU and 20000 IU only) and purified water

The 800 IU, 1000 IU and 3200 IU strengths are dose proportional. The 20000 IU and 25000 IU strengths are also 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 or almost 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 the drug substance is present in solution in the finished product.

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

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

Quality control of drug substance
The active substance specification is 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 methyl formate stated on the CEP is adopted by the MAH. 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 5°C ± 3°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 5°C ± 3°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. The intended use of the lowest strength in paediatric population has been adequately justified.
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 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 is made to the Ph. Eur. and United States Pharmacopeia. 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 cholecalciferol, average fill weight, average total weight, disintegration, loss on drying, uniformity of dosage units by mass variation, assay cholecalciferol, identification of butylhydroxytoluene, assay of butylhydroxytoluene, 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. Satisfactory validation data for the analytical methods have been provided. 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 for three production scaled batches per strength 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. A photostability study showed that the capsules are sensitive to light when exposed to light directly. On basis of the data provided a shelf-life could be granted of 24 months when stored in the original package, 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 and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cholecalciferol INVOS 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

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 calcaemic hormone, but it is now clear that vitamin D metabolites have also 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 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 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 (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).

<u>Vitamin D3 and autoimmune diseases – mice</u>
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 faeces 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-sensitising 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 diarrhoea. 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 Cholecalciferol INVOS soft capsules, are safe and generally regarded as non-toxic in the concentrations used.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Cholecalciferol INVOS 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 INVOS 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

An limited pharmacokinetics overview has been provided, however from these data it may be expected that the pharmacokinetics are comparable, taking into account the comparison of the pharmaceutical form and ingredients of the product to be marketed and those mentioned in literature. Moreover, the proposed formulation, does not contain critical excipients. From a clinical point of view, it is agreed with the MAH 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.
The MAH has provided an overview of general pharmacodynamic properties of vitamin D. Section 4.5 of the SmPC reflects the interactions of vitamin D with other medicinal products. The pharmacodynamic section is considered sufficiently described.

IV.2 Clinical efficacy

800, 1000 & 3200 IU strengths

The MAH submitted several studies to support the proposed indication and posology for treatment of vitamin D deficiency. These studies used a variety of dosing schedules to investigate to achieve normal 25(OH)D levels after a certain period of treatment including loading doses and/or several weeks or months of treatment.

Appropriate doses to be considered are in the range of 800-4000 IU/day as also indicated for instance in NL SmPCs of the Benferol (NL/H/3500/001-003, national authorisation number: RVG 117092) and Will Pharma (NL/H/2963/001-004, national authorization number: RVG 113925) products. After first month, lower doses should be considered, dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment.

Osteoporosis

For the adjunct therapy of osteoporosis a daily dose of 800 - 1,000 IU is proposed by the MAH. It is agreed the daily dose of 800 IU – 1000 IU mentioned for osteoporosis is acceptable and equivalent to the already approved SmPCs. According to the authorised SmPC of Will Pharma (NL/H/2963/001-004, national authorisation number: RVG 113925) the maximum dose for osteoporosis is 2000 IU/day in adults and elderly with osteoporosis.

20000 & 25000 IU strengths

In this section, the MAH combined abstracts of several articles. Most articles studied the effect of weekly or monthly dosing regimens, which revealed effective results on 25OHD. Based on the major objections raised by CMSs, the MAH decided to restrict the indication of 20000 IU and 25000 IU to the initial treatment for vitamin D deficiency which is acceptable. The MAH proposed a weekly dose of 20000 IU or 25000 IU. After one month a lower maintenance dose should be considered. This is acceptable although a loading dose of 100000 IU at once has been accepted in the Netherlands as well.

Treatment with vitamin D deficiency in adolescents

In alignment with the authorised SmPC of Will Pharma (NL/H/2963/001-004, national authorization number: RVG 113925) and the SmPC of cholecalciferol mibe 1000 IU (DE/H/3562/002), in adolescents 12-18 years a daily dose 800 IU-1000 IU is recommended for the prevention of vitamin D deficiency. For the initial treatment of vitamin D deficiency in adolescents the maximum dose should not exceed 4000 IU/day (SmPC Divisun 4000 IU, SE/H/1122/004).

Overall, the MAH summarises 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 SmPC of vitamin D products.

IV.3 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.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cholecalciferol INVOS 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.5 Discussion on the clinical aspects

The MAH summarised 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 Cholecalciferol INVOS is considered positive.

V. USER CONSULTATION

The MAH has provided a bridging report. For content, the proposed package leaflet (PL) was compared to the PL of a comparable product (Colecalciferol 20,000 IU). This product was approved in 2017 in the United Kingdom. It can be concluded that the content of both PLs is comparable. For design/layout, the proposed PL uses the design/layout of another product of the same MAH (Rabeprazole GAP), approved in procedure PT/H/0881/01-02/DC. Both content and layout are bridged to approved PLs. No additional user testing is required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cholecalciferol INVOS 800 IU, 1000 IU, 3200 IU, 20000 IU and 25000 IU soft capsules have a proven chemical-pharmaceutical quality. Cholecalciferol INVOS 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 Cholecalciferol INVOS, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 August 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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