COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cholecalciferol IBSA 25.000 IU orodispersible film (cholecalciferol (vitamin D3))

NL/H/5787/001/DC

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This module reflects the scientific discussion for the approval of Cholecalciferol IBSA 25.000 IU orodispersible film. The procedure was finalised on 21 August 2024. 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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cholecalciferol IBSA 25.000 IU orodispersible film, from IBSA Farmaceutici Italia S.r.l.

The product is indicated for: initial treatment of clinically relevant vitamin D deficiency (serum levels < 25 nmol/l or < 10 ng/ml) in adults.

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

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

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of cholecalciferol (vitamin D3). For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Cholecalciferol (vitamin D3) 25.000 IU was first introduced into the European market at least ten years ago as a preoperative medication for the treatment of vitamin D deficiency.

In accordance with part II of Annex I of Directive 2001/83, regarding article 10a applications, the MAH has sufficiently submitted bridging data to demonstrate that the product applied for is similar to the product(s) described in literature.

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

II. QUALITY ASPECTS

II.1 Introduction

Cholecalciferol IBSA is a rectangular, flexible, opaque light orange film.

Each film contains as active substance 625 micrograms cholecalciferol (vitamin D3) equivalent to 25 000 IU.

The excipients are: refined olive oil, purified water, maltodextrin, hydroxypropylbetadex, copovidone, mannitol (E421), glycerin (E422), polysorbate 80 (E433), glycerol monolinoleate, titanium dioxide (E171), sucralose (E955), orange flavour*, ascorbic acid (E300), all-rac-α-tocopherol (E307), and sunset yellow (E110).
*it contains:

Aromatic Part: orange essential oil, terpeneless orange oil, terpeneless lemon oil, terpeneless mandarin oil, ethyl hexanoate, ethy 2-methylbutyrate, ethyl butyrate and acetaldehyde

Additives: butylated hydroxyanisole (E320), citric acid (E330).

Carriers: maltodextrin, acacia gum (E414)

The orodispersible films are packed in polyethylene terephthalate/aluminium/polyethylene (PET/Aluminium/PE) laminate sachets.

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 crystalline powder and it is practically insoluble in water, freely soluble in ethanol (96%), and soluble in trimethylpentane and in fatty oils. The polymorphic form is not relevant, as the finished product is present in 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. The supplementary test stated on the CEP has been adopted by the MAH. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Several formulations were tested based on two patents for orodispersible films. Selection of a flavour was also tested. Optimisation of the film flexibility is done by introducing

copovidone. Improvement of dissolution and introduction of surfactant and antioxidants were investigated. Further optimisation of the formulation was evaluated by adjusting the ratio cholecalciferol and cyclodextrin.

Manufacturing process

The main steps of the manufacturing process are mixing, drying, formation of rolls, cutting , final film formation and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches of the wet mass in accordance with the relevant European guidelines. The wet mass batches were split up for further drug product manufacture of the different strengths.

Control of excipients

The excipients, except orange flavour and colourant E110 sunset yellow comply with Ph.Eur. requirements. In-house specifications for orange flavour and colourant sunset yellow are provided. The specifications for the excipients 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, size (surface area), average weight, identity and assay of vitamin D3 (cholecalciferol), uniformity of dosage units, impurities, identity and assay of vitamin E, identity and assay of vitamin C, loss on drying, dissolution, sealing of the sachet and microbial control. Except for assay of vitamin D3, vitamin E and vitamin C, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scale batches 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 four production scale batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable ICH guidelines demonstrating the stability of the product for 24 months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are 'Do not store above 30°C. Store in the original package in order to protect from light'.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cholecalciferol IBSA 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 Introduction

The nonclinical overview was adequately drafted based on the available literature on pharmacology, pharmacokinetics and toxicology of vitamin D3 (cholecalciferol), that is available in the public domain, in form of textbooks, published papers and regulatory data sheets. Additional nonclinical studies are not needed.

III.2 Pharmacology

Vitamin D3 is produced by the body starting from 7-dehydrocholesterol (provitamin D3) in the skin, when it is exposed to sunlight, and converted into vitamin D3 (Wacker & Holick, 2013), which is translocated from the epidermis into the circulation by the vitamin D-binding protein (DBP).
The principal biological function of vitamin D3 is to maintain serum calcium and phosphorus concentrations within the normal range by enhancing the efficiency of the small intestine to absorb these minerals from diet. The 1,25(OH)2D3 enhances the efficiency of intestinal calcium absorption. The 1,25(OH)2D3 also enhances the phosphorus absorption in jejunum and ileum.
Vitamin D3 has numerous biological functions, including modulation of cell proliferation, differentiation and apoptosis, neuromuscular, hormone and immune function, as well as other physiological processes (Sintov et al., 2014). Vitamin D3 deficiency causes decreased ionised calcium concentrations in blood and a resultant increase in the production and secretion of parathyroid hormone (PTH). PTH stimulates the mobilisation of skeletal calcium, inhibits renal excretion of calcium, and stimulates renal excretion of phosphorus resulting in normal fasting serum calcium concentrations and low or near-normal serum phosphorus.
The effects of a vitamin D3 deficiency on bone metabolism are well known. Calcium and bone homeostasis are tightly linked, as calcium is a major constituent of the bone and provides strength to the skeleton, but the bone is also the largest store of calcium in the body (Christakos et al., 2016). In adults, a vitamin D3 deficiency results in osteomalacia and osteoporosis, and in children to rickets.

III.3 Pharmacokinetics

The pharmacokinetic (PK) of vitamin D3 and its derivatives is well known in humans. There are limited PK data in animals. Vitamin D3 and its analogues are readily absorbed from the gastrointestinal (GI) tract following oral administration. After absorption, vitamin D3 enters the blood via chylomicrons of lymph, and it is then associated mainly with specific α-globulin (vitamin D-binding protein, DBP). The hydroxylated metabolites of cholecalciferol 1(OH)D3, 1,25(OH)2D3 and 24,25(OH)2D3) also circulate associated with the same α-globulin.
In the liver, vitamin D3 is converted in the mitochondria to its 25-hydroxy derivative, 25(OH)D3. Vitamin D3 25-hydroxylase activity is regulated in the liver by the plasma concentrations of vitamin D3 and its metabolites. In the kidneys, these metabolites are further hydroxylated to their active form, the 1,25(OH)2D3 (calcitriol) (AHFS, 2007).
The circulating half-life of the 25-hydroxy metabolite ranges between 10 days and 3 weeks; the half-life of the 1,25(OH)2D3 is about 4-6 hours. The metabolites of vitamin D3 are excreted mostly in bile and faeces. Although some vitamin D3 that is excreted in bile is reabsorbed in the small intestine, enterohepatic circulation does not appear to play an important role for conservation of the vitamin (AHFS, 2007).

III.4 Toxicology

The acute (single-dose) toxicity of cholecalciferol appears to be low with LD50 ranging between 42 and 80 mg/kg after oral administration, to the different animal species (Eason, 1993; Makita et al., 1976). The most frequent findings in the repeated dose toxicity studies are an increased concentration of calcium and a reduced concentration of phosphates in urines, as well as proteinuria (Makita et al., 1976). At higher doses, hypercalcemia is also observed. The most frequent observed histological alterations (i.e. calcification) involve kidney, heart, aorta, testes, thymus and intestinal mucosa, as a result of a prolonged condition of hypercalcemia (Mortensen et al., 1993). However, there is a wide margin of safety between the human recommended therapeutic doses and the doses that induce toxicity in animals.
The studies of reproductive toxicity show that cholecalciferol has no detrimental effects on fertility and reproduction. At doses that are superimposable to the human recommended therapeutic doses, cholecalciferol is not teratogenic but cholecalciferol overdosage in animals has been shown to induce malformations in rats, mice and rabbits at doses significantly higher than the human dose (i.e. 4-15 times the human dose) (McClain et al., 1980). Studies on mutagenesis or carcinogenesis are not available from literature but there is no evidence of an increased risk of cholecalciferol for mutagenesis and carcinogenesis.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. This will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.6 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 (vitamin D3) is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

In general, the literature data regarding the pharmacokinetic properties of cholecalciferol are adequately summarised by the MAH.

IV.3 Pharmacodynamics

The pharmacodynamics of cholecalciferol is well-established and has been adequately summarised by the MAH. No new data have been submitted, which is acceptable given the legal basis under which it has been submitted.

Primary pharmacology
Vitamin D exists in two forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is found in plants, being the product of UVB (290 to 315 nm) irradiation of ergosterol; it can be consumed as a supplement or fortified foods. Vitamin D3, a product of UVB irradiation of 7-dehydrocholesterol, is synthesised in the human epidermis or consumed in the form of oily fish, fortified foods, or a supplement (Holick, 2006).
Vitamin D is converted in the liver to 25(OH)D, which is the major circulating metabolite of vitamin D. In the kidney, 25(OH)D is then converted by 1α-hydroxylase to its active form, 1,25-dihydroxyvitamin D [1,25(OH)2D], which plays a vital role in maintaining bone and muscle health by regulating calcium metabolism. The activity of the vitamin D 1α-hydroxylase enzyme requires molecular oxygen, magnesium ion and malic acid, and it is primarily regulated by the parathyroid hormone (PTH) in response to low serum concentrations of calcium and phosphate (Holick 2006; Holick & Chen, 2008).
The effects of vitamin D are mediated by an intracellular vitamin D receptor (VDR). Circulatory 1,25(OH2)D crosses the cell membrane and cytoplasm and reaches the nucleus, where it binds to the VDR. The VDR-bound 1,25(OH2)D in turn binds to the retinoic acid x-receptor and serves as a nuclear transcription factor, altering gene function and inducing protein synthesis. The 1,25(OH2)D-VDR complex triggers an increase in GI absorption of both calcium and phosphorus. In addition, vitamin D is involved in bone formation, resorption, and mineralisation and in maintaining neuromuscular function. Circulating 1,25(OH)2D reduces serum PTH levels directly by decreasing parathyroid gland activity and indirectly by increasing serum calcium. The 1,25(OH)2D also regulates bone metabolism in part by interacting with

the VDR in osteoblasts to release biochemical signals, leading to formation of mature osteoclasts. These reabsorb bone tissue with secondary release of calcium and phosphate into the circulation. In addition, either directly or indirectly, 1,25(OH)2D regulates over 200 genes, including those involved in renin production in the kidney, insulin production in the pancreas, release of cytokines from lymphocytes, production of cathelicidin in macrophages, and growth and proliferation of both vascular smooth muscle cells and cardiomyocytes (Lee et al., 2008).
The functional outcomes of effects related to the interaction between vitamin D status and calcium intake have been extensively investigated. These effects fall into three broad categories: 1) synergistic effects of vitamin D status and calcium intake on calcium absorption; 2) effects of calcium intake on vitamin D status; and 3) largely observational data suggesting an association between calcium and vitamin D status and non-skeletal outcomes, such as cancer (Heaney, 2008).

Secondary pharmacology

In recent years, vitamin D has received increased attention due to the resurgence of vitamin D deficiency and rickets in developed countries and the identification of extra-skeletal effects of vitamin D, suggesting unexpected benefits of vitamin D in other health and diseases to those linked to bone health. Although the potential extra-skeletal effects of vitamin D3 are beyond the scope of the present application, there is a further considerable range of functions for vitamin D and potential therapeutic implications outside of calcium homeostasis and bone health, highlighting the increased understanding of vitamin D, as well as how much is yet to be learned. The possibility of extra-skeletal effects of vitamin D was first noted with the discovery of the VDR in tissues and cells that are not involved in maintaining mineral homeostasis and bone health, including skin, placenta, pancreas, breast, prostate and colon cancer cells, and activated T cells. However, the biological significance of the expression of the VDR in different tissues is not fully understood, and the role of vitamin D in extra-skeletal health has been a matter of debate (Christakos et al., 2013).
Receptors for calcitriol are distributed widely throughout the body. The non-classic actions of vitamin D can be categorised into three general effects: regulation of hormone secretion, regulation of immune function, and regulation of cellular proliferation and differentiation. Because of these effects, ecological and observational studies suggest that low vitamin D status could be associated with higher mortality from life-threatening conditions including cancer, cardiovascular disease, and diabetes mellitus that account for 60% to 70% of total mortality in high-income countries (Autier & Gandini, 2007).
From a molecular mechanism of action perspective, recent research has indicated that the genomic mechanism of 1,25(OH)2D3 action involves the direct binding of the 1,25(OH)2D3 activated VDR/retinoic X receptor (VDR/RXR) heterodimeric complex to specific DNA sequences. Numerous VDR co-regulatory proteins have been identified, and genome-wide studies have shown that the actions of 1,25(OH)2D3 involves the regulation of gene activity at a range of locations many kilobases from the transcription start site. CYP2R1 has been identified as the most important 25-hydroxylase, and a critical role for CYP24A1 in humans was noted in studies showing that inactivating mutations in CYP24A1 are a probable cause of idiopathic infantile hypercalcemia. In addition, studies using knockout and transgenic mice have provided new insight on the physiological role of vitamin D in classical target tissues as well as evidence of extra-skeletal effects of 1,25(OH)2D3 including inhibition of cancer progression, effects on the cardiovascular system, and immunomodulatory effects in certain autoimmune diseases. Some of the mechanistic findings in mouse models have also been

observed in humans. The identification of similar pathways in humans could lead to the development of new therapies to prevent and treat disease (Christakos et al., 2016).
The potential role for vitamin D and its active metabolite 1,25(OH)2D3 in modulating the immune response was outlined by the fact that vitamin D deficiency is a well-known accompaniment of various infectious diseases such as tuberculosis, and 1,25(OH)2D3 has long been recognised to potentiate the killing of mycobacteria by monocytes (Martineau et al., 2011).
In recent years, 1,25(OH)2D3 has been evaluated for its potential anticancer activity in animal and cell studies for approximately 25 years. The epidemiological evidence supporting the importance of adequate vitamin D nutrition (including sunlight exposure) for the prevention of a number of cancers is extensive (Bikle, 2009).
Some data suggest that a large proportion of the US men had suboptimal vitamin D status (especially during the winter/spring season), and both 25(OH)D and 1,25(OH)2D may play an important role in preventing prostate cancer progression. Moreover, vitamin D status, measured by 25(OH)D in plasma, interacts with the VDR FokI polymorphism and modifies prostate cancer risk. Men with the less functional FokI ff genotype (14% in the European-descent population of this cohort) are more susceptible to this cancer in the presence of low 25(OH)D status (Li et al., 2007).
In the last decades there has been an effort to understand possible roles of vitamin D, including its role in the immune system and, in particular, on T cell-medicated immunity. Vitamin D receptor is found in significant concentrations in the T lymphocyte and macrophage populations. However, its highest concentration is in the immature immune cells of the thymus and the mature CD-8 T lymphocytes. The significant role of vitamin D compounds as selective immunosuppressants is illustrated by their ability to either prevent or markedly suppress animal models of autoimmune disease. Results show that 1,25(OH)2D3 can either prevent or markedly suppress experimental autoimmune encephalomyelitis, rheumatoid arthritis, systemic lupus erythematosus, type I diabetes, and inflammatory bowel disease. The vitamin D hormone stimulates transforming growth factor beta-1(TGFβ-1) and interleukin 4 (IL-4) production, which in turn may suppress inflammatory T cell activity (Deluca & Cantorna, 2001). The common denominator that rises from these studies is that vitamin D affects the immune system at many levels and by a number of mechanisms. Initial observations indicate that vitamin D supplementation may be preventive in multiple sclerosis and diabetes mellitus. Furthermore, vitamin D inhibits epidermal proliferation and promotes epidermal differentiation and therefore is a potential treatment for psoriasis vulgaris. Vitamin D also affects the function of skeletal muscle, brain, and blood pressure (Friedman, 2011).

Dose finding

At present, there is an ongoing debate on how much vitamin D is needed to achieve a protecting effect against osteoporosis, cancer and other diseases. The daily recommended dose in vitamin D replete subjects has substantially changed and it now ranges from 600-800 IU/day (IOM 2010) to 800-2.000 I.U/day (Dawson-Hughes et al., 2010; IOF, 2009), with vitamin D maximum daily intakes in the range of 4.000 -10.000 I.U. being considered safe (IOM, 2010). The recommended daily dose is depending on the 25(OH)D3 target levels to be achieved, which is 20 ng/ml for the US IOM (IOM 2010) and 30 ng/ml for the IOF (IOF, 2009). The IOM position, pertaining to the North America setting, is mainly driven by the large use of vitamin D supplemented foods widely available in the US.

Vieth (Vieth, 1999) believes people need 4.000-10.000 I.U. vitamin D daily and that toxic side effects are not a concern until a 40.000 I.U. per day dose. Reports of other experts in the field are in line with these findings. It has been suggested by several experts that older adults, sick adults, and "perhaps all adults" would need 800-1.000 I.U. vitamin D daily and it has been indicated that daily doses of 2.400 I.U. (i.e. four times the recommended intake) can be consumed safely. According to recent estimations an intake of 1.000 I.U. daily would bring25(OH)D3 serum levels of at least 50% of the population up to advantageous ranges of 30 ng/ml (Bischoff-Ferrari, 2008). Thus, higher doses of vitamin D are needed as oral supplements, at least for those individuals who do not reach the desired ranges.

According to numerous studies documenting the magnitude of the effect of sun exposure, the primitive intake would have been at least 4.000 I.U./day, with corresponding serum 25(OH)D3 levels ranging from 40 to 80 ng/ml (Heaney & Holick, 2011).

With regard to the dosage options that can be used to achieve target serum 25(OH)D3 levels, a review that examined the results of 11 studies in a total of 449 elderly subjects (Byrne et al., 1995) has shown that the mean concentration of 25(OH)D3 reached on low-dose continuous supplementation ranged from 22.8 to 42 ng/ml compared to slightly lower levels (22 to 34.8 ng/ml) following high-dose supplementation. With both dose regimens, the mean values fall within the physiological range for young adults.

Another recent study (Hin et al., 2017) has evaluated the effects of daily supplementation with vitamin D3 4.000 I.U., 2.000 I.U. or placebo for 1 year on biochemical markers of vitamin D status in 305 community-dwelling people aged ≥ 65 years. Mean (SD) plasma 25(OH)D levels were 50 (18) nmol/L at baseline and increased to 137 (39), 102 (25) and 53 (16) nmol/L after 12 months in those allocated 4000 I.U., 2.000 I.U. or placebo, respectively (with 88%, 70% and 1% of these groups achieving the pre-specified level of >90 nmol/L). Neither dose of vitamin D3 was associated with significant deviation outside the normal range of PTH or albumin-corrected calcium. Supplementation with vitamin D had no significant effects on cardiovascular risk factors or on measures of physical function. The results of this study suggested that daily 4000 I.U. vitamin D3 is effective to achieve blood levels associated with lowest disease risks.

However, the use of high intermittent dose of vitamin D3 given as a dose equivalent to daily 4000 I.U. has proved to be effective in the normalisation of serum 25(OH)D3 levels. In a recent study (Delomas et al., 2017), 111 nursing home residents (mean age 85.1 ± 6.7 years) were randomly assigned to either 100.000 x 4 I.U. every 2 weeks (treated group) or an individualised regimen according to baseline 25(OH)D3 level (control group). Irrespective of treatment group, at the 7th day after the last dose of cholecalciferol, 100% of residents reached serum values ≥20 ng/ml, and 93.6 vs. 88.2% reached values ≥30 ng/ml in the treatment and control group respectively. While mean value was higher in the treatment group (50.2 ± 615.4 vs. 35.8 ± 66.5 ng/ml; p<0.0001), none of participants had seen their value >150 ng/ml. This study showed that a single dose of 400.000 I.U. every 2 weeks is at least as effective and safe as tailored regimen in terms of the ability to rapidly normalise 25(OH)D3 values.

Similarly, another study (Wijnen et al., 2015) in 30 nursing home patients with 25(OH)D levels <50 nmol/l who were randomised to receive vitamin D3 in divided doses of 50.000 I.U. twice a week, followed by a monthly maintenance dose of either 50.000 or 25.000 I.U. (loading dose group) or 800 I.U. daily (daily dose group) for 26 weeks, showed that levels of 25(OH)D >75 nmol/L at week 5 were reached in 79 % of the 14 loading dose patients, but in none of the 13 daily dose patients (p<0.001). At week 26, 25(OH)D levels >75 nmol/L were reached in 83 % of the 12 loading dose patients and in 30 % of the 10 daily dose patients (p<0.05). In this study

in nursing home patients with severe 25(OH)D deficiency, an individualised calculated cholecalciferol loading dose was likely to be superior to a daily dose of cholecalciferol 800 I.U. in terms of the ability to rapidly normalise vitamin D levels.
The effects of a single, high, oral dose of vitamin D3 (120.000 I.U.) on circulating serum levels of vitamin D3 and metabolites in elderly were investigated in a recently published study (Leszczyńska et al., 2022) that included 58 patients aged from 61 to 96 years old. After administration, 56.6% of patients attained a serum 25(OH)D3 concentration >30 ng/ml and all except one achieved a serum 25(OH)D3 concentration >20 ng/mL. None exceeded the reference value of vitamin D3 (30-50 ng/mL). 24,25(OH)2D3 concentration gradually grew, achieving the highest concentration on 7th day. The percentage increase of 25(OH)D3 was negatively correlated with baseline 25(OH)D3 ($r = -0.688$, $p = 0.001$). None of the study participants developed hypercalcemia. The baseline concentration of vitamin D metabolites analysed in serum and their percentage increase were neither dependent on BMI nor on the percentage of fat tissue. In this study, a single high dose of vitamin D rapidly enhanced 25(OH)D3 serum concentration in elderly patients.
In the view of the recent debates on the most appropriate vitamin D3 requirements for the prevention and management of vitamin D3 deficiency, the high-dose intermittent supplementation may be considered as an effective alternative regimen to the low-dose continuous dosing for preventing hypovitaminosis D, particularly in elderly subjects. The intake of a sufficient dose of vitamin D and an improved adherence to supplementation are the two main factors to be taken into consideration to ensure desirable vitamin D levels for fall and fracture prevention.

IV.4 Clinical efficacy

Supplementation with cholecalciferol is to be considered as well-established for the treatment of vitamin D deficiency. The MAH has adequately summarised the bibliographical efficacy data in the clinical overview. Cholecalciferol is widely used and the effectiveness in the proposed indication is well known and sufficiently discussed in the provided literature. In particular, the available literature has consistently shown that intermittent high dose supplementation of vitamin D, given at intervals as a function of the unit dose, reduces the incidence of fractures in patients of senile osteoporosis and corrects the vitamin D deficiency in conditions such as chronic kidney disease or rickets.
The effects of high-dose administration of vitamin D in the reduction of risk of fractures has been demonstrated in clinical trials that included elderly populations of either sex treated with 100.000 I.U. of cholecalciferol given every 4 months (Trivedi et al., 2003), in elderly resident who were not vitamin D deficient according to standard definitions receiving an initial dose of vitamin D3 10.000 I.U. once weekly and then 1.000 I.U. daily (Flicker et al., 2005), and in elderly osteoporotic patients treated with annual IM injection of vitamin D 150.000-300.000 I.U. (Heikinheimo et al., 1992). A single injection of 300.000 units of vitamin D2 was effective in increasing BMD and in reducing the risk of falls in women who underwent hip fracture (Harwood et al., 2004). A vitamin D dose of 20.000 I.U./week given for 9 months during the initial replenishment phase and followed by a 15-month randomised maintenance phase was effective to replenish vitamin D stores in haemodialysis patients (Tokmak et al., 2008). In a further study (Chandra et al., 2008), a dose of 50.000 I.U. of cholecalciferol given once weekly for 12 weeks was effective in raising serum 25(OH)D levels and reducing PTH levels in patients with CKD.

The adequacy of an intensive high-dose administration of vitamin D (intensive phase with 100.000 I.U. every 2 weeks followed by 100.000 I.U. in the every other month maintenance phase) in normalising 25(OH)D and PTH levels was demonstrated in another study (Courbebaisse et al., 2009) in renal transplant patients with low 25(OH)D and normal serum calcium levels. Finally, in a study in haemodialysis patients (Wasse et al., 2012), treatment with cholecalciferol 200.000 I.U./week for 3 weeks was associated with a high rate of patients who achieved serum 25(OH)D concentrations ≥ 30 ng/ml. The efficacy of high-dose calciferol has also been demonstrated in children with nutritional rickets secondary to a dietary deficiency of vitamin D or inadequate exposure to sunlight. A vitamin D dose of 1.200.000 I.U. (600.000 I.U. at enrolment and at 12 weeks) alone or in combination with calcium (Thacher et al., 1999) was used with success in the treatment of children with rickets. These results were confirmed in another study (Thacher et al., 2014), in which children with active rickets treated with oral vitamin D2 50.000 I.U. once a month for 6 months. In a more recent study (Mittal et al., 2014), children with clinical and radiologically confirmed rickets treated with oral vitamin D3 as 300.000 I.U. or 600.000 I.U. in a single day underwent radiological healing and significant fall in the serum PTH and alkaline phosphatase levels. Because of the peculiar PK characteristics of vitamin D and its long-term storage in the lipophilic compartments of the human body, cholecalciferol can be either administered with high frequency of administration, such as daily (1.000 I.U.) or as alternate days (2.000 I.U.), or every week (6.000 I.U.), but also at high dosages, such as 25.000, 50.000 or 100.000 I.U., given at intervals ranging from 2 weeks up to 8 months depending on the dose, age range and population to be treated. All these dosages are adequate to maintain serum 25(OH)D3 concentrations within the required range.
The subsections below have been focused on the most recent trials that have contributed to support the adequacy of high-dose administration of vitamin D in achieving and maintaining the target serum 25(OH)D3 levels. Despite the recommendations of the recent IOM report (IOM, 2010) on dietary reference intakes for calcium and vitamin D, there is still continued controversy over what constitutes the normal range of serum 25(OH)D levels and what the appropriate vitamin D dose should be to achieve these levels. Recent findings suggest that the dosage of vitamin D supplementation generally recommended in guidelines may be insufficient in patients with vitamin D deficiency, and that higher daily dosages may be necessary. The availability of the proposed formulation that is the object of the present application (Vitamin D3 25.000 I.U. ODF) may represent a valuable option to meet these requirements, in the respect of dose recommended by guidelines, but with the possibility of better tailoring the dose on the basis of individual requirements, and with improved adherence to therapy.

IV.5 Clinical safety

The MAH has adequately summarised the bibliographical safety data in the clinical overview. In general, vitamin D is well tolerated. However, there is a risk for toxicity, especially with higher dosages. Hypercalcaemia is the main adverse event.

The precautions of use in other special populations are sufficiently addressed in the SmPC.

IV.6 Risk Management Plan

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

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

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies described in the literature. No new clinical studies were conducted.

Risk management is adequately addressed. The clinical aspects of this product are approvable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test with three participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cholecalciferol IBSA 25.000 IU orodispersible film has a proven chemical-pharmaceutical quality. Cholecalciferol IBSA has an adequate efficacy and safety profile and is considered widely established.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Cholecalciferol IBSA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 August 2024.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5787/001/IA/001	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: for an active substance; or for a starting material/reagent/intermediate used in the manufacturing process of the active substance; or for an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. ○ New certificate from a new manufacturer (replacement or addition)	No	11-11-2024	Approved	N/A
NL/H/5787/IA/002/G	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product • Minor change in the manufacturing process.	No	17-03-2025	Approved	N/A
NL/H/8787/001/WS/003	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Primary packaging site Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Site where any manufacturing operation(s) take place, except batch-	No No No	02-04-2025	Approved	N/A

	release, batch control, primary and secondary packaging, for non-sterile medicinal products. Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a manufacturer responsible for importation and/or batch release ○ Including batch control/testing 3x Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product • Minor change in the manufacturing process	Yes No			
NL/H/5787/ 001/P/001	Artikel 61(3): to introduce a change in the paragraph 5 of the PL	Yes	16-04-2025	Approved	N/A