Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Choli-D3 10,000 IU Capsules, soft
Choli-D3 50,000 IU Capsules, soft

(Colecalciferol)

PL 48836/0012-0013

Osgen Pharmaceuticals Limited

LAY SUMMARY

Choli-D3 10,000 IU Capsules, soft
Choli-D3 50,000 IU Capsules, soft
(Colecalciferol)

This is a summary of the Public Assessment Report (PAR) for Choli-D3 10,000 IU and 50, 000 IU Capsules, soft. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Choli-D3 soft capsules in this lay summary for ease of reading.

For practical information about using Choli-D3 soft capsules, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Choli-D3 soft capsules and what are they used for?
These applications are for medicines that have a well-established use. This means that the use of the active substance in these medicines has been well-established in the UK for at least 10 years, with recognised efficacy and an acceptable level of safety.

Choli-D3 10,000 IU Capsules, soft are used for treatment and prevention of Vitamin D deficiency and as an adjunct to specific therapy for osteoporosis in adult and elderly patients with vitamin D deficiency.

Choli-D3 50,000 IU Capsules, soft are used in the treatment of Vitamin D3 deficiency.

How do Choli-D3 soft capsules work?
Choli-D3 soft capsules contain the active substance colecalciferol (Vitamin D3). Vitamin D helps the body to absorb calcium and is also essential for bone formation and normal bone metabolism. Vitamin D is found in the diet and is also produced in the skin after exposure to the sun. Often vitamin D is given in combination with calcium.

How are Choli-D3 soft capsules used?
The pharmaceutical form of this medicine is a soft capsule and the route of administration is oral (taken by mouth).

The dose prescribed for the patient will depend on their risk of developing vitamin D deficiency, level of vitamin D in their blood and their response to treatment.

The usual recommended dose is:
Adults
Choli-D3 10,000 IU Capsules
Prevention of vitamin D deficiency: 1 capsule every 2 weeks or 1 capsule weekly for those at high risk of vitamin D deficiency (see below).

Treatment of vitamin D deficiency: 2 capsules weekly for up to 4-12 weeks.

Higher doses can be necessary depending on severity of the deficiency and the patient´s response to treatment.

Choli-D3 50, 000 IU soft capsules:
The patient's doctor will usually prescribe 1 capsule every week for 6-8 weeks, followed by a maintenance and prevention therapy of 1 capsule every 2 months.

Children and adolescents
Choli-D3 soft capsules are not suitable for children and adolescents (under 18 years of age).

Method of administration
The patient should swallow the capsules whole with water, they should not chew the capsules.

Choli-D3 soft capsules should be taken with the main meal of the day.

For further information on how Choli-D3 soft capsules are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

What benefits of Choli-D3 soft capsules have been shown in studies?
As the active substance, colecalciferol, has been in clinical use for over 10 years, data were provided in the form of literature references to show that:

- Choli-D3 10,000 IU soft capsules are safe and efficacious in the treatment and prevention of Vitamin D deficiency and as an adjunct to specific therapy for osteoporosis in adults and elderly patients with vitamin D deficiency.
- Choli-D3 50,000 IU soft capsules are safe and efficacious in the treatment of Vitamin D3 deficiency.

What are the possible side effects of Choli-**D3 soft capsules?**
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

Why were Choli-D3 soft capsules approved?
It was concluded that the data provided from literature references had shown that:

(i) Choli-D3 10,000 IU Capsules, soft are effective in the treatment and prevention of Vitamin D deficiency and as an adjunct to specific therapy for osteoporosis in adult and elderly patients with vitamin D deficiency.
(ii) Choli-D3 10,000 IU Capsules, soft are effective in the treatment of Vitamin D3 deficiency.

Furthermore, the well-established use of the active substance colecalciferol has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Choli-D3 soft capsules?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Choli-D3 soft capsules. The RMP details the important risks of Choli-D3 soft capsules, how these risks can be minimised, any uncertainties about Choli-D3 soft capsules (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Choli-D3 soft capsules:

Important identified risks	• Hypersensitivity, including allergic reactions to Colecalciferol or any excipients. • Hypercalcaemia • Hypercalciuria • Interaction with thiazide diuretics • Interaction with cardiac glycosides • Use in patients with conditions that modify vitamin D metabolism, including sarcoidosis • Use in patients with hypervitaminosis D • Use in patients with renal impairment (including nephrolithiasis or nephrocalcinosis)
Important potential risks	• Use in pregnancy and lactation • Overdose
Important missing information	• None

The information included in the SmPCs and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Choli-D3 soft capsules are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided for these medicines and are satisfactory.

Other information about Choli-D3 soft capsules
Marketing authorisations for Choli-D3 soft capsules were granted in the United Kingdom (UK) on 22 December 2022.

The full PAR for Choli-D3 soft capsules follows this summary.

This summary was last updated in May 2023.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Choli-D3 10,000 IU and 50, 000 IU Capsules, soft (PL 48836/0012-0013) could be approved.

Choli-D3 10, 000 IU Capsules, soft is approved in adults and the elderly for:
- the treatment and prevention of vitamin D deficiency.
- as an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency.

Choli-D3 50, 000 IU Capsules, soft is approved in adults and the elderly for:
- the treatment of vitamin D3 deficiency.

In its biologically active form colecalciferol (also known as Vitamin D3), the active substance, stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue. In the small intestine it promotes rapid and delayed calcium uptake. The passive and active transport of phosphate is also stimulated. In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular resorption. The production of parathyroid hormone (PTH) in the parathyroid is inhibited directly by the biologically active form of vitamin D3. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active Vitamin D3.

These applications were approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as well-established use applications. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the United Kingdom (UK) on 22 December 2022.

II QUALITY ASPECTS

II.1 Introduction

These products contain 10, 000 IU or 50,000 IU colecalciferol (equivalent to 250 or 1250 micrograms Vitamin D3) in each soft capsule.

In addition to colecalciferol, these products also contain the excipients medium chain triglycerides and all-rac-α-Tocopheryl acetate (Vitamin E acetate) in the capsule fill. The capsule shells contain gelatin; glycerol; sorbitol liquid, partially dehydrated; brilliant Blue FCF (Color FD & C Blue 1) (E133; the 10,000 IU strength capsule only) and purified water.

The finished products are packaged in polvinylchloride/polyvinylidene chloride/aluminium (PVC/PVdC/aluminium) blisters, in the follow pack sizes:

10,000 IU strength capsules:
4 , 5, 7, 10, 14, 15, 20, 30, 50, 60, 90 and 100 soft capsules.

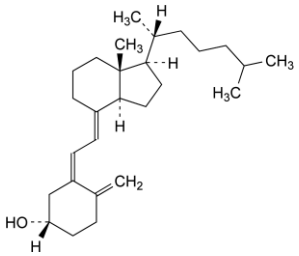
50,000 IU strength capsules:
3, 4, 6, 8, 10, 20 and 30 soft capsules

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Colecalciferol
Chemical Name: (3S,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3-ol
Molecular Formula: $C_{27}H_{44}O$
Chemical Structure:



Molecular Weight: 384.6g/mol
Appearance: It is a free-flowing, reddish-brown powder.

Colecalciferol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin, no excipients of animal or human origin are used in the finished products. EDQM certificates have been provided for the excipient gelatin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 48 months (10 000 IU strength capsule only) and 36 months (50,000 IU strength capsule only), with the storage conditions 'Store the capsules in the original container in order to protect from light.', is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
These applications were submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as well-established use applications. No new non-clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology
No new pharmacology data were submitted, and none were required for these applications.

The pharmacology of vitamin D is well known and described in the literature, and the review provided in the dossier is sufficiently detailed and is adequate.

A brief summary of the non-clinical pharmacology of colecalciferol as presented by the applicant is provided below.

Primary pharmacodynamics
Vitamin D exists in two forms: as colecalciferol (Vitamin D3) and ergocalciferol (Vitamin D2).

Colecalciferol is produced by animal skin due to the action of ultraviolet radiation (290-310 nm) on 7-dehydrocholesterol. Ergocalciferol is found in plant sources; it differs from D3 only in having a 22, 23 double bond and having an additional methyl group attached to carbon 24.

Both forms of vitamin D are biologically inactive prohormones that must undergo successive hydroxylations at carbons 25 and 1 before they can bind to and activate the vitamin D receptor.

Colecalciferol is first hydroxylated to 25-hydroxyvitamin D3 [25(OH)D3, or calcidiol] in the liver and then to the active form, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3, or calcitriol] in the kidney by the enzyme vitamin D 1α-hydroxylase. Calcitriol enhances the intestinal

absorption of calcium. Ergocalciferol (vitamin D2) undergoes the same two-stage activation process, involving first 25-hydroxylation in the liver to form 25(OH)D2 followed by 1α-hydroxylation in the kidney to form the biologically active molecule 1,25(OH2)D2. Colecalciferol (vitamin D3) and ergocalciferol (vitamin D2) together are described as vitamin D.

The main mechanism of action of vitamin D is the interaction of 1,25(OH)D with the nuclear vitamin D receptor (VDR), which heterodimerises with retinoid X receptor (RXR) and acts as a ligand-activated transcription factor by binding to genomic vitamin D responsive elements (VDRE) in vitamin D-regulated genes. These include more than 50 other genes important for mineral homeostasis, vitamin D metabolism, energy metabolism, cell differentiation and proliferation, extracellular matrix proteins, oncogenes, growth factors, signal transduction proteins and peptide hormones. Genes can be upregulated or downregulated. Amongst the genes that are downregulated are PTH, osteocalcin, protein-kinase A inhibitors and interleukin-2 genes.

Colecalciferol induced soft tissue calcification at 1 and 10 μg/kg administered orally in rape seed oil by gavage to young Fü-albino rats from Days 3 to 6 of lactation. Bone calcium mobilisation and intestinal calcium absorption was as expected high after intrajugular injection of 12.5 ng/kg. Some vitamin D analogues tested show higher activity than colecalciferol and competed to a similar degree in binding to 1,25-dihydroxyvitamin D3 (colecalciferol) receptors of rat intestine.

It was reported that the active metabolite of colecalciferol, 1,25(OH)2D3, was 30 times more potent than 1,24(OH)2D2 in stimulating intestinal calcium absorption in vitamin-D deficient rats, but both moieties had similar potencies in stimulating bone calcium mobilisation. In cultured mouse bone cells, 1,25(OH)2D3 and 1,24(OH)2D2 were equipotent in stimulating osteoclast formation and bone resorption. Overall, the active metabolite of colecalciferol, 1,25(OH)2D3, has greater calcaemic activity *in vivo*.

Vitamin D deficiency/insufficiency is defined based on circulating calcidiol [25(OH)D3] levels in serum.

Secondary pharmacodynamics

Numerous functions of the skin are regulated by vitamin D and/or its receptor. These include inhibition of proliferation, stimulation of differentiation including formation of the permeability barrier, promotion of innate immunity, regulation of the hair follicle cycle, and suppression of tumour formation. The VDR ligand, 1, 25 dihydroxyvitamin D3 (1,25(OH)2D3), reduces proliferation and enhances differentiation, and thus has been investigated for a role in preventing or treating cancer.

A paper describes the suppression by 1,25-(OH)2D3 of the growth of human cancer cell-derived xenografts in immune-suppressed mice. This study examined the dose-dependent response for inhibition of tumour growth in transgenic mice with retinoblastoma and evaluates the in vivo toxicity of the vitamin D3 analogue 1,25-(OH)2-16-ene-23-yne vitamin D3 (16,23-D3)-D3 in non-transgenic mice. Transgenic 8-10-week-old mice with retinoblastoma (n = 119) were randomly assigned to groups receiving 1.0, 0.75, 0.5, 0.35, 0.2, or 0.05 μg of 16, 23-D3 and a vehicle alone (control) group intraperitoneal (i.p.) five times a week for 5 weeks. In the dose-response study, tumour growth inhibition was greatest in the group receiving 0.35 μg (55% inhibition; P = 0.0056) and was also significant in the group receiving 0.5 microg (42% inhibition; P = 0.036). The systemic toxic effects due to hypercalcemia occurred at doses of ≥1.0 μg. 16,23-D3 inhibits tumour growth at doses ≥ 0.35

μg and shows toxic effects at doses ≥1.0 μg related to hypercalcemia in mice fed an unrestricted diet.

Vitamin D exhibits anticancer effects, perhaps through inhibition of angiogenesis, this was demonstrated in VDR deficient mice where effects on VDR expression was examined. 1, 25(OH)2D3 treatment was important in modulating VDR expression which plays a significant role during retinal vascular development.

The suppression of the renal 1α,25-dihyroxyvitamin D3 (1α,25-(OH)2-D3) production in aP2-agouti transgenic mice by increasing dietary calcium decreases adipocyte intracellular Ca2+ ([Ca2+]i), stimulates lipolysis, inhibits lipogenesis, and reduces adiposity has been reported.

The active vitamin D metabolite, 1,25-dihydroxyvitamin D3[1,25-(OH)2D3], exerts immunosuppressive activity. A study reported that renin expression and plasma angiotensin II production were increased several fold in VDR-null mice, leading to hypertension, cardiac hypertrophy, and increased water intake. Hence, 1,25(OH)2D3 is a negative endocrine regulator of the renin-angiotensin system. Its apparent critical role in electrolytes, volume, and blood pressure homeostasis suggests that vitamin D analogues could help prevent or ameliorate hypertension.

Interaction with VDR, 1,25-dihydroxyvitamin D3 mediates numerous biological activities, such as regulation of helper T-cell development and subsequent cytokine secretion profiles. Variants of the VDR have been found to be associated with immune-mediated diseases that are characterised by an imbalance in helper T-cell development, such as Crohn's disease and tuberculosis. The VDR, hence, is a good candidate to be investigated for association with asthma, which is characterised by enhanced helper T-cell type 2 activity.

Studies have summarised the biological evidence implicating a potential influence of vitamin D on glucose homeostasis. Vitamin D deficient rabbits and mice present with impaired insulin secretion, and supplementation with vitamin D corrects the defect.

There is growing evidence that Vitamin D3 (1,25-dihydroxyvitamin D3) is involved in brain development. Vitamin D-deficient female rats were mated with vitamin D normal males. Pregnant females were kept vitamin D-deficient until birth whereupon they were returned to a control diet. At week 10, protein expression in the progeny’s prefrontal cortex and hippocampus was compared with control. Developmental vitamin D (DVD) deficiency caused a dysregulation of 36 brain proteins involved in several biological pathways including oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, chaperoning, post-translational modifications (PTMs), synaptic plasticity and neurotransmission.

A study used a rat model of nerve trauma to demonstrate that vitamin D acts on myelination. In this study the rat left peroneal nerve was cut and autografted in an inverted position. Immediately after lesioning, the animals were treated with either colecalciferol or ergocalciferol (100-500 IU/kg/day for 12 weeks). The data indicated that colecalciferol is a more potent neuromodulator than ergocalciferol. colecalciferol increased the number of preserved or newly formed axons in the proximal end, the mean axon diameter in the distal end and neurite myelination in both distal and proximal ends. The authors concluded that colecalciferol improved myelination and recovery after nerve injury.

Colecalciferol and its active metabolite calcitriol may also reduce the risk of developing cancer. The beneficial anti-cancer effects of dietary vitamin D3 and calcitriol in mouse xenograft models of breast and prostate cancer was investigated. After ingestion of a vitamin D3 supplemented diet (5000 IU/kg for 4 weeks) significant tumour shrinkage was observed in mice bearing MCF-7 breast cancer xenografts and PC-3 prostate cancer xenografts. Similar results were observed after the administration of calcitriol. The authors concluded that estrogen synthesis and signalling and other pro-inflammatory and growth signalling pathways were suppressed by dietary vitamin D3 and calcitriol in mouse xenograft models of breast and prostate cancer. This demonstrates the potential use of vitamin D3 in the treatment and prevention of cancers such as breast and prostate cancer. In addition, in another study colecalciferol (10,000 IU/kg in the diet) decreased cell proliferation and increased cell death in clear cell renal cell carcinoma xenografted mice. This demonstrates its therapeutic potential in renal cell carcinoma.

Additional studies have shown that the active metabolite of vitamin D3 [calcitriol 1,25(OH)2D3] possesses potent anti-cancer properties, affecting tumour progression in animal models by a number of mechanisms including anti-proliferation, anti-angiogenesis, pro-apoptosis, pro-differentiation and anti-inflammation.

Safety pharmacology

It has been reported that vitamin D derivatives exhibit restricted access across the rat blood-brain-barrier, therefore having minimum effects on the central nervous system. The role of vitamin D3 (2 IU/g in the diet for 6-9 weeks) in regulating cardiovascular function was also investigated in vitamin-D deficient Sprague-Dawley rats. The authors reported that vitamin D3 deficiency was associated with increased systolic blood pressure and increased rate of cardiac contractility, although there were no effects on heart rate. The data from the study concluded that vitamin D3 plays an important role in maintaining normal cardiovascular function. In contrast to these beneficial cardiovascular effects, another study which used very high doses of colecalciferol over a short duration of time (100,000 IU for 3 days) to induce cardionecrosis in rats. However, the authors did report that most rats recover from the vitamin D-induced cardionecrosis and also the dose that produces cardionecrosis exceeds three times the minimal dose causing a noticeable Ca^{2+} increase.

Pharmacodynamic drug interactions

Glucocorticoids are known to be vitamin D antagonists. A study was undertaken to establish the effect of glucocorticoids on vitamin D metabolism in young male Wistar rats. This study found that cortisol treatment in rats is associated with decreased accumulation of the dihydroxylated derivative of vitamin D ($1,25(OH)_2D_3$) in intestinal mucosa cells and kidney cells. the decrease in $1,25(OH)_2D_3$ in intestinal mucosa cells and kidney cells led to a subsequent decrease in the concentration of the vitamin D-dependent intestinal CaBP resulting in a hypocalcaemic effect of glucocorticoids.

Published studies have claimed that cortisone influences the metabolism of vitamin D_3. This study found that a higher concentration of the active metabolite (25-hydroxycholecalciferol) was detected in the plasma of the cortisone-treated rats than in the controls.

The effect of chronic phenobarbital treatment (75mg/kg/day administered intraperitoneally for 4 or 8 weeks) on the metabolism of vitamin D by rat liver has been reported in a study using 3-week-old Sprague-Dawley rats. The data of this study indicated that chronic phenobarbital therapy decreased both the release of 25(OH)D from the liver and the efficiency of hepatic 25(OH)D production. The authors reported that these mechanisms, in

particular the inhibition of 25(OH)D release from the liver, may be responsible for the low levels of 25(OH)D seen during long-term phenobarbital therapy.

Ketoconazole, which inhibits the 24-hydroxylase activity, markedly enhances the potency of calcitriol. Enhanced potency of calcitriol is also seen in 24-hydroxylase null mice. There is an increased risk of hypercalcaemia if colecalciferol is co-administered with thiazide diuretics and calcium. Plasma-calcium concentrations should be monitored in patients receiving the drugs concurrently. Some antiepileptics may increase vitamin D requirements (e.g., carbamazepine, phenobarbitone, phenytoin, and primidone).

Colecalciferol requirements may also be increased by the following medicines: barbiturates, cholestyramine, colestipol, hydantoin anticonvulsants, mineral oil, and primidone. A case of severely decreased prothrombin has been reported due to a possible interaction of colecalciferol with warfarin and calcium carbonate.

III.3 Pharmacokinetics

No new pharmacokinetic data were submitted, and none were required for these applications.

The pharmacokinetic properties of colecalciferol are well known, have been reported in published and are adequately in the applicant's non-clinical overview. A summary of the pharmacokinetic profile of colecalciferol is provided below.

Absorption

Colecalciferol is well absorbed after oral administration, mainly from the small intestine. Colecalciferol is a relatively non-polar molecule and needs to be solubilised by incorporation into bile-salt micellar solutions for absorption to occur via the gastro-intestinal tract. Absorption of [^{3}H]-vitamin D in normal subjects was shown to be 62-91% of the dose. Various conditions in humans can reduce its absorption e.g., coeliac disease, biliary obstruction absorption, chronic pancreatitis, liver failure, cystic fibrosis, Crohn's disease and gastric bypass.

Distribution

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Metabolism

Vitamin D requires metabolic activation by hydroxylation in the liver through the enzyme 25-hydroxylase to calcidiol, the major circulating form of vitamin D. Calcidiol is further hydroxylated in the kidney to calcitriol, the biologically active form of colecalciferol. In addition to the kidney, final activation to calcitriol may also occur at other sites, including keratinocytes and macrophages. The enzyme catalysing this last step, Vitamin D 1α-hydroxylase, is subject to tight regulatory control.

The vitamin D_3 activating cytochrome P450s are CYP2R1, CYP27A1 and CYP27B1 and the catabolic cytochrome P450 is CYP24A1. There are differences between humans and rats in the CYP24A1-dependent metabolism of $1\alpha,25(OH)_2D_3$. CYP24A1 is integrally involved in

the degradation of 25-hydroxyvitamin D3 and $1\alpha,25(OH)_2D_3$ through side-chain hydroxylation and cleavage known as C-24 oxidation.

Further metabolism of calcidiol and calcitriol occurs in the kidneys by 24-hydroxylase, including the formation of the 1, 24, 25-trihydroxy derivative.

Excretion
Colecalciferol is mainly excreted via the bile in faeces, with a small amount excreted via urine. There is a small amount of enterohepatic recycling, but this is considered to have a negligible effect on vitamin D status.

Pharmacokinetic drug interactions
A pharmacokinetic interaction between vitamin D3 and digoxin in mice was investigated. In the study, vitamin D3-treated mice were given an intravenous bolus dose of radio-labelled $^{[3H]}$ digoxin (0.1mg/kg). The vitamin D3-treated mice showed decreased blood and brain concentrations of digoxin as a result of increased renal and total body clearance.

III.4 Toxicology

Single-dose and Repeated-dose toxicity
The lethal dose in dogs is stated to be 13 mg/kg body weight. Immediate effects are bloody diarrhoea, anorexia, thirst, polyuria and prostration. In surviving animals calcium is deposited as in chronic hypervitaminosis D.

The acute toxicity of colecalciferol in the European rabbit (Oryctolagus cuniculus) was evaluated. An initial dose-ranging acute toxicity study was carried out with doses of 50-400mg/kg in 16 rabbits. A second acute toxicity study on 39 rabbits used doses of 3.5-30mg/kg to determine the minimum dose of colecalciferol that causes mortality in rabbits. It was observed that in the initial dose-ranging study, within 2-5 days of being dosed all 16 rabbits died. Most deaths in this second study occurred between 4-8 days after dosing, and the clinical signs of toxicity observed included lost appetite and bodyweight.

Colecalciferol (vitamin D3)-related changes in a 26-week, repeated-dose oral toxicity study in rats consisted of nephrocalcinosis and pheochromocytomas in the adrenal medulla. These changes were observed at doses $\geq$ 5000 IU/kg/day.

Colecalciferol was more toxic in Rhesus monkeys than ergocalciferol. Daily doses of 50,000 IU, 100,000 IU and 200,000 IU of colecalciferol or ergocalciferol were given and all receiving colecalciferol developed hypercalcaemia, died within 16 to 160 of the start of the study and had extensive soft tissue mineralisation and nephrocalcinosis.

Genotoxicity
Calcitriol, the hormonal metabolite of colecalciferol, was not genotoxic in the microbial mutagenesis assay with or without metabolic activation, and in an *in vivo* micronucleus assay in mice.

In-vitro salmonella/microsome tests (Ames tests) and chromosomal aberration tests using a Chinese hamster fibroblast cell line have been conducted on various food additives including colecalciferol. The results of mutagenicity screening of colecalciferol were negative in both the Ames tests and chromosomal aberration tests.

Carcinogenicity
The carcinogenic potential of colecalciferol has not been studied in rodents.

In a review paper, carcinogenicity and genotoxicity data from medicinal products for human use authorised via the European centralised procedure between 1995 and 2009 were evaluated, including data on a drug product containing the active substance. The authors of this paper reported that colecalciferol is devoid of genotoxic potential.

Reproductive and developmental toxicity
Vitamin D has been reported to be teratogenic in animals at 4-15 times the recommended human dose. Offspring from pregnant rabbits treated with high doses of vitamin D had lesions anatomically similar to those of supravalvular aortic stenosis and offspring not showing such changes show vasculotoxicity similar to that of adults following acute vitamin D toxicity. The symptoms are most likely due to hypercalcaemia.

In developmental toxicity investigations in the rat, there were no significant effects on litter sizes, resorption rates, pup weights and external, visceral and skeletal abnormalities. There were no adverse effects on fertility or pup development, although hypercalcaemia was observed in pregnant females and pups treated with 0.08 and 0.3 μg/kg/day.

In rabbits treated with 0.3 μg/kg/day colecalciferol, 3 out of 16 pregnant female rabbits died with 2 showing histopathological evidence of hypervitaminosis D (focal renal tubular calcification). Clinical signs of toxicity included maternal weight loss, increased resorption rate and neonatal mortality.

Other toxicity studies
None

Studies on impurities
No toxicological concerns were raised.

III.5 Ecotoxicity/Environmental Risk Assessment
The applicant has provided adequate justification for not submitting an Environmental Risk Assessment (ERA) for colecalciferol: it is a vitamin and as such is unlikely to result in significant risk to the environment following approval of the marketing authorisations for the proposed products. This is acceptable.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of colecalciferol are well-known. The overview based on a literature review and a review of these studies is, thus, satisfactory.

IV. 2 Pharmacokinetics
The pharmacokinetics of colecalciferol are relatively well known.

The pharmacokinetics of vitamin D3 do not follow a simple absorption, metabolism, excretion pathway. Storage of vitamin D3 and its metabolites in body fat result in slow elimination from the body. The main pharmacokinetic features are summarised below.

Absorption
Dietary or supplemented vitamin D is absorbed from the small intestine by passive diffusion. The efficient absorption of vitamin D is dependent upon the presence of fat in the intestinal lumen, which triggers the release of bile acids and pancreatic lipase. In turn, bile acids initiate the emulsification of lipids, pancreatic lipase hydrolyses the triglycerides into monoglycerides and free fatty acids, and bile acids support the formation of lipid-containing micelles, which diffuse into enterocytes. Early studies have also demonstrated that radio-labelled vitamin D3 appeared almost exclusively in the lymphatics and in the chylomicron fraction of plasma. Subjects with impaired bile acid release or pancreatic insufficiency have demonstrated significantly reduced vitamin D absorption**.**

Distribution
Colecalciferol and its metabolites circulate in the blood bound to a specific globulin called vitamin D-binding protein. Vitamin D-binding protein (DBP) is a multi-functional plasma protein, belonging to the albumin superfamily of binding proteins. The plasma concentration of DBP ranges from 4-8μM. In the plasma, DBP acts to bind and transport vitamin D metabolites throughout the body, interacting with 25(OH)D3 with an affinity of between 5×10- 8 to 1×10-11M. Apart from in the plasma, DBP has also been detected in cerebrospinal fluid, seminal fluid, saliva and breast milk. Approximately 88 ± 3% and 83 ± 8% of 25(OH)D3 is bound to serum vitamin D-binding protein (DBP) in healthy and cirrhotic subjects, respectively.

Metabolism
Colecalciferol is hydroxylated in the liver to form 25-hydroxy-cholecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1, 25-dihydroxycholecalciferol (calcitriol).

The major metabolite of vitamin D3 is 25(OH)D3, also known as calcidiol. This is the major circulating form of vitamin D, and it is transported in the blood to the kidney by a class of proteins called vitamin D binding proteins (DBP) that are specific for vitamin D and its metabolites. In the proximal renal tubule of the kidney, 25(OH)D3 is hydroxylated at C1 in the A ring to form the hormonally active from of vitamin D, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), which is responsible for most if not all of the biological activity of vitamin D. The cytochrome P450 monooxygenase 25(OH)D3 1α hydroxylase (CYP27B1; 1α(OH) that is responsible for the metabolism of 25(OH)D3 to 1,25(OH)2D3 is present predominantly in the kidney, but it is also found in other extra-renal sites. This specific aspect of the metabolism is meditated via the NADP-ferrodoxin reductase enzyme system. In addition to the 1,25(OH)2D3 metabolite, the kidney also produces 24,25-dihydroxyvitamin D3 (24,25(OH)2D3), a relatively inactive metabolite when compared to 1,25(OH)2D3. The 25-hydroxyvitamin D3 24 hydroxylase (CYP24) enzyme can also hydroxylate both 25(OH)D3 and 1,25(OH)2D3. However, 1,25(OH)2D3 is the preferred substrate for 24(OH)ase when compared to 25(OH)2D3. Thus, 24(OH)ase accelerates the catabolism of 1,25(OH)2D3 to 1,24,25(OH)3D3 resulting in calcitroic acid or by producing 24,25(OH)2D3 and thereby decreasing the pool of 25(OH)D3 available for 1-hydroxylation**.**

Excretion
The metabolites circulate in the blood bound to a specific α – globin, Vitamin D3 and its metabolites are excreted mainly in the bile and faeces. The primary excretion route of vitamin D is via the bile into the feces. More specifically, 1, 25-dihydroxyvitamin D3 is excreted in the bile as polar metabolites, such as glucuronides and, possibly sulfates and neutral polar steroids. These compounds undergo an entero-hepatic recirculation in both man and experimental animals.

Vitamin D is principally excreted in the bile. Some of the metabolites (1,25-dihydroxyvitamin D3 and 24,25-dihydroxyvitamin D3) is reabsorbed in the small intestine and re-excreted in the bile. One of the active metabolites (1,25-dihydroxyvitamin D3) is present in bile as a glucosiduronate of 1,25-dihydroxyvitamin D3. Animal studies also confirm that metabolites are excreted in the bile as a glucuronide form. However, since vitamin D is metabolised to more water-soluble compounds, a variety of vitamin D metabolites, most notably calcitroic acid, are excreted by the kidney into the urine. Metabolites are eliminated primarily (96%) through the bile and faeces. Colecalciferol 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. Calcidiol has an experimental elimination half-life of 19 days. The lipophilic nature of vitamin D explains its adipose tissue distribution and its slow turnover in the body (half-life ≈2 mo). Its main transported metabolite, 25-hydroxyvitamin D3 [25(OH)D3], shows a half-life of ≈15 d, whereas the 1α,25(OH)2D3 has a half-life of ≈15 hours.

Bioavailability in special populations

Renal impairment

A 57% lower metabolic clearance rate is reported in subjects with renal impairment as compared with that of healthy volunteers. The absorption and metabolism of vitamin D3 has been studied in 8 patients (aged 21-40 years) with chronic renal disease (CRD) using preparations of radioactive vitamin D (vitamin D3 1,2- 3H). Healthy adult volunteers of similar ages (29-32 years) were also used for this study for comparison. All subjects received 8-10 μc of vitamin D3 1,2-3H (D3-3H), dissolved in 1.1 ml of ethanol, 1 hour before breakfast and after a 12-15 hour overnight fast. The dose was delivered onto the tongue from a calibrated syringe. The D3-3H was then rinsed down with 250 ml of milk. Blood, urine and faecal samples were obtained and analysed for radioactivity. After the oral dose of D3-3H, peak plasma D3-3H levels were in each instance lower than normal in patients with CRD. The mean±SE plasma D3-3H half-times for normal and CRD subjects were 27.8±1.0 and 13.2±1.1 hrs, respectively. This difference was highly significant with $P<0.001$.

The mean cumulative urinary excretion of radioactivity for the 72-hr period after the oral D3-3H dose in 5 control subjects was 1.69% of the administered dose. The total 72-hour urinary radioactivity in CRD subjects averaged 0.34% of the administered dose. The "net" absorption of D3-3H, calculated by assuming that the D3-3H not recovered in the faeces had been absorbed, normally averaged 90.2%. The distribution of faecal radioactivity and "net" D3-3H absorption in CRD subjects did not significantly deviate from normal values. Based on the overall findings of this study, the authors reported that the intestinal absorption of vitamin D3-3H was normal in patients with CRD. However, the metabolic fate of the vitamin was abnormal as characterised by an increase in the fractional turnover rate of vitamin D3 in plasma, an abnormal accumulation of biologically inactive lipid-soluble vitamin D3 metabolites, and an abnormal urinary excretion of both vitamin D3-3H and biologically inactive metabolites. The study provides evidence that the metabolism and excretion of vitamin D is abnormal in patients with renal disease.

Hepatic impairment

The intestinal absorption of (3H) colecalciferol was studied in five patients with alcoholic liver disease, six patients with primary biliary cirrhosis, and 15 healthy subjects. The rate of appearance in plasma of (3H) colecalciferol after oral ingestion and the subsequent appearance of (3H) polar metabolites in the alcoholic subjects were similar to those in the healthy subjects.

In subjects with primary biliary cirrhosis, the rate of appearance in plasma of (3H) colecalciferol was significantly reduced. The rate of appearance of labelled polar metabolites of colecalciferol was also lower in this group, suggesting that increased removal of labelled vitamin by conversion into more polar metabolites could not account for the reduced plasma (3H) colecalciferol response. It is suggested that intestinal absorption of colecalciferol is usually normal in alcoholic liver disease but impaired in primary biliary cirrhosis. Hepatic 25- hydroxylation is normal in alcoholic liver disease but may be defective in primary biliary cirrhosis. Mild to moderate hepatic dysfunction can also cause malabsorption of vitamin D, but production of calcidiol is possible. However, dysfunction of 90% or more resulted in the inability to make sufficient calcidiol. Another study found that the intestinal absorption of colecalciferol in patients with mild cholestasis was similar to normal healthy subjects. However, patients with severe cholestasis absorbed negligible amounts of colecalciferol. Also, the intestinal absorption and hepatic 25-hydroxylation of colecalciferol is found to be normal in patients with alcoholic liver disease but may be impaired in primary biliary cirrhosis.

Age
The capacity of the kidney to convert 25(OH)D3 to 1,25(OH)2D3 has been reported to decline with age. An increase in 24(OH)ase gene expression and an increase in clearance of 1,25(OH)2D3 with aging have been reported.

Race
Cross-sectional and longitudinal analyses were conducted with the use of data from two placebo-controlled, randomised trials at two academic medical centres in the United States. A total of 208 subjects (black and white American adults) with pre- or well- controlled diabetes with a mean age of 59.1 y were randomly assigned to receive daily colecalciferol supplementation doses of 2000 or 4000 IU or a matching placebo for 16 weeks. Colecalciferol supplementation increased total and measured free 25(OH)D concentrations proportionally to the dose and without a difference between races. The relation between free and total 25(OH)D did not vary systematically by race in this multiracial population with pre- or well-controlled diabetes.

Sixteen-week randomised controlled trial was conducted to assess the effects of vitamin D3 (colecalciferol) vs 25-hydroxyvitamin D3 (calcifediol) on total and free 25D in a multi-ethnic cohort of adults (35 adults; ≥18 years of age).The doses used were 60 µg (2400 IU)/d of D3 or 20 µg/d of 25D3.The study concluded that 25D3 increased total and free 25D levels more rapidly than D3, regardless of race/ethnicity.

In a randomised controlled trial, women with a singleton pregnancy at 12–16 weeks' gestation received 400, 2000 or 4000 IU vitamin D3/day until delivery. The primary outcome was maternal/neonatal circulating 25(OH)D at delivery, with secondary outcomes 25(OH)D ≥80 nmol/L achieved, and 25(OH)D concentration required to achieve maximal 1,25(OH)2D production. There were no differences between groups on any safety measure. Not a single adverse event was attributed to vitamin D supplementation or circulating 25(OH)D levels. Vitamin D supplementation of 4,000 IU/day for pregnant women was safe and most effective in achieving sufficiency in all women and their neonates regardless of race while the current estimated average requirement was comparatively ineffective at achieving adequate circulating 25(OH)D, especially in African Americans.

The data presented above signals of no significant effect of race on the pharmacokinetics of vitamin D3; however certain populations like dark skinned individuals are at high risk of vitamin D deficiency, and may require higher doses and monitoring of serum 25(OH)D.

Drug-Drug interactions
A study investigating the effects of prednisone on vitamin D metabolism in four normal adult subjects reported that synthetic glucocorticoids antagonise the action of vitamin D. The effects of concomitant prednisone administration on vitamin D metabolism included a rapid turnover of vitamin D3, a diminished production of a biologically active metabolite and the subsequent decrease in the intestinal absorption of calcium.

Concomitant use of Vitamin D with anticonvulsants (such as phenytoin) or barbiturates (and possibly other drugs that induce hepatic enzymes) may reduce the effect of Vitamin D3 by metabolic inactivation.

In cases of treatment with thiazide diuretics, which decrease urinary elimination of calcium, monitoring of serum calcium concentration is recommended. The cytotoxic agent actinomycin and imidazole antifungal agents interfere with Vitamin D3 activity by inhibiting the conversion of 25-hydroxyVitamin D3 to 1,25- dihydroxyVitamin D3 by the kidney enzyme, 25-hydroxyVitamin D3-1-hydroxylase.

Serum levels of colecalciferol may be reduced by concomitant administration of calcium channel blockers, cimetidine, gabapentin, heparin, hydroxychloroquine, indapamide, isoniazid, neomycin, or valproic acid. Treatment with orlistat has reportedly reduced mean serum vitamin D levels in adolescents prescribed a multivitamin. Orlistat augments weight-loss through its effects on fat; therefore, it may also prevent the absorption of fat-soluble vitamins such as vitamin D. Consequently, patients administered weight-loss drugs are strongly recommended to increase vitamin D supplementation and regularly monitor vitamin D status.

Colecalciferol lowers plasma concentrations and AUC of atorvastatin when administered concomitantly. Atorvastatin is extensively metabolised by CYP3A4; therefore, an increase in vitamin D-mediated CYP3A4 activity in the gut and liver may be responsible for the decrease in atorvastatin bioavailability.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of vitamin D are well-known. No new pharmacodynamic data have been submitted for this application and none were required. The applicant has provided, in the clinical overview, the literature reviews of the possible physiological influence of vitamin D in a variety of clinical conditions.

A summary of the pharmacodynamics profile of colecalciferol is provided below.

Mechanism of action
The principal biological function of vitamin D is the maintenance of normal levels of serum calcium and phosphorus in the bloodstream by enhancing the efficacy of the small intestine to absorb these minerals from the diet.

The active form of vitamin D3 (calcitriol) binds to intracellular receptors that then function as transcription factors to modulate gene expression. Like the receptors for other steroid hormones and thyroid hormones, the vitamin D receptor has hormone-binding and DNA-binding domains. The vitamin D receptor forms a complex with another intracellular receptor, the retinoid-X receptor, and that heterodimer is what binds to DNA. In most cases studied, the effect is to activate transcription, but situations are also known in which vitamin D suppresses transcription. Calcitriol increases the serum calcium concentrations by increasing GI absorption of phosphorus and calcium, increasing osteoclastic resorption, and

increasing distal renal tubular reabsorption of calcium. Calcitriol appears to promote intestinal absorption of calcium through binding to the vitamin D receptor in the mucosal cytoplasm of the intestine. Subsequently, calcium is absorbed through formation of a calcium-binding protein. Once absorbed from the intestine, colecalciferol is metabolised in the liver to 25-hydroxyvitamin D [25(OH)D3] (also called calcidiol). 25(OH)D3 is subsequently converted to its active form of 1,25-dihydroxyvitamin D [1,25(OH)2D3] (also known as calcitriol), in the kidney, by the action of 1α-hydroxylase enzyme. The enzyme is also distributed in a number of extra-renal sites such as in immune cells, in the epithelia of many tissues, in bone, and in the parathyroid glands. In these tissues the enzyme functions to provide calcitriol for local consumption as an intracrine or paracrine factor. In humans, these extra-renal sources of 1,25(OH)2D3 only contribute significantly to the levels of 1,25(OH)2D3 circulating during pregnancy, in chronic renal failure, and in certain pathological conditions such as sarcoidosis, tuberculosis, granulomatous disorders, and rheumatoid arthritis.

The active metabolite, 1, 25(OH)2D, acting through vitamin D receptors (VDR) can produce a wide range of skeletal and non-skeletal effects. 1, 25(OH)2D acts either synergistically with PTH or alone and modulates calcium homeostasis and bone metabolism. 1,25(OH)2D maintains calcium balance, the regulation of PTH, the promotion of the renal reabsorption of calcium, increased intestinal absorption of calcium and phosphorus, and increased calcium and phosphorus mobilization of calcium and phosphorus from bone to plasma to maintain balanced levels of each in bone and the plasma. Evidence in the laboratory also indicates that 1, 25(OH)2 D3 has a number of non-skeletal effects including, inhibition of autoimmune diseases and cancer progression, modulation of immune system, and regulation of cardiovascular system and adipocyte apoptosis.

Calcitriol functions to maintain normal concentrations of calcium and phosphate in plasma by facilitating their absorption in the small intestine, by interacting with parathyroid hormones to enhance their mobilisation from bone, and by decreasing their renal excretion. The characteristics of calcitriol are those of a hormone, and consequently vitamin D is a pro-hormone rather than a true vitamin. The structure of calcitriol is similar to that of other steroid hormones. As long as sunlight exposure is adequate, calcitriol can be produced by the body without the need for vitamin D dietary supplementation. Like other hormones, calcitriol circulates at picogram concentrations that are 1000 times less than those of its precursor calcidiol. Based on the need for increased calcium absorption, the synthesis of calcitriol is closely regulated and stimulated primarily by the serum parathyroid hormones, and by low serum calcium or phosphorus levels, and inhibited by circulating FGF23 produced by osteocytes. Calcitriol is produced in the kidney, distributes via the circulation system to its site of action in the intestinal cell to increase calcium absorption or in the bone to stimulate differentiation and activation of osteoblasts and osteoclasts.

Pharmacodynamic effects

A study investigated the quantitative relation between steady state colecalciferol input and the resulting serum 25-hydroxycholecalciferol concentration and to estimate the proportion of the daily requirement during winter that is met by colecalciferol reserves in body tissue stores. Colecalciferol was administered daily in controlled oral doses labelled at 0, 25 (1000 IU), 125 (5000 IU), and 250 (10,000 IU) μg colecalciferol for approximately 20 weeks during the winter to 67 men living in Omaha (41.2 °n latitude). The time course of serum 25-hydroxycholecalciferol concentration was measured at intervals over the course of treatment. from a mean baseline value of 70.3 nmol/l, equilibrium concentrations of serum 25-hydroxycholecalciferol changed during the winter months in direct proportion to the dose, with a slope of approximately 0.70 nmol/l for each additional 1 μg colecalciferol input. The

calculated oral input required to sustain the serum 25-hydroxycholecalciferol concentration present before the study (i.e., in the autumn) was 12.5 μg (500 IU)/d, whereas the total amount from all sources (supplement, food, tissue stores) needed to sustain the starting 25-hydroxycholecalciferol concentration was estimated at approximately 96 μg (approximately 3800 IU)/d. By difference, the tissue stores provided approximately 78-82 μg/d. Healthy men seem to use 3000-5000 IU colecalciferol/d, apparently meeting > 80% of their winter colecalciferol need with cutaneously synthesised accumulations from solar sources during the preceding summer months. It is reported that current recommended vitamin D inputs are inadequate to maintain serum 25-hydroxycholecalciferol concentration in the absence of substantial cutaneous production of vitamin D.

The relative potencies of vitamins D2 and D3 were evaluated by administering single doses of 50,000 IU of the respective calciferols to 20 healthy male volunteers, following the time course of serum vitamin D and 25-hydroxyvitamin D (25OHD) over a period of 28 days and measuring the area under the curve of the rise in 25OHD above baseline. The two calciferols produced similar rises in serum concentration of the administered vitamin, indicating equivalent absorption. Both produced similar initial rises in serum 25OHD over the first three days, but 25OHD continued to rise in the D3-treated subjects, peaking at 14 days, whereas serum 25OHD fell rapidly in the D2-treated subjects and was not different from baseline at 14 d. Area under the curve (AUC) to day 28 was 60.2 ng. d/ml (150.5 nmol.d/litre) for vitamin D2 and 204.7 (511.8) for vitamin D3 ($P < 0.002$). Calculated AUC (infinity) indicated an even greater differential, with the relative potencies for D3:D2 being 9.5:1. Vitamin D2 potency is less than one third that of vitamin D3. It was stated that physicians resorting to use of vitamin D2 should be aware of its markedly lower potency and shorter duration of action relative to vitamin D3.

IV.4 Clinical efficacy

No new efficacy data have been submitted for these applications and none were required. The clinical efficacy of colecalciferol is well-established. Efficacy is adequately reviewed in the clinical overview; a summary relevant to the proposed indications and posology is also provided.

Vitamin D Insufficiency

Vitamin D insufficiency is a term that has been used to describe the finding of biochemical evidence of deficiency, without obvious clinical signs or symptoms, such as rickets or osteomalacia. The condition is most commonly diagnosed by a measuring serum 25(OH)D level. There is an inconsistency, however, in the definition of threshold. At a symposium on Vitamin D insufficiency, insufficiency was reportedly defined as a 25(OH)D level below 40 nmol/L (16 μ/L). Although there is no consensus on optimal levels of 25(OH)D as measured in serum, vitamin D deficiency is defined by most experts as a 25(OH)D level of less than 20 ng/mL (50 nmol/L). Experts agree that a minimum 25(OH)D serum concentration of 30 ng/mL (75 nmol/L) appears necessary to experience the multitude of beneficial health effects of vitamin D.

Treatment and prevention of vitamin D deficiency

A double blind, unicentre, randomised, placebo-controlled study evaluated the changes in 25-hydroxyvitamin D (25(OH)D) serum levels in 150 young Belgian adults (18-30 years), monthly supplemented with 50,000 IU of vitamin D or placebo for 6 months. At time 0 (months), 30% of the population presented 25(OH)D serum levels below 20 ng/mL. In the vitamin D-treated group, mean serum levels increased from 21.2 ± 8.2 to 30.6 ± 8.8 ng/mL ($P < 0.001$) at time 3 months and to 36.0 ± 9.2 ng/mL ($P < 0.001$) at 6 months. Despite documented vitamin D intake, no changes in serum levels were, however, observed in 10%

of the treated group. In the placebo group, mean 25(OH)D serum levels decreased from 22.8 ± 8.5 to 14.0 ± 6.9 ng/mL at T3 mo ($P < 0.001$) but returned to values not significantly different from those observed at T0 (23.5 ± 8.6 ng/mL) at T6mo. No difference between serum calcium levels was observed between the groups throughout the study. In conclusion, monthly supplementation with 50,000 UI of vitamin D in winter can warrant serum 25(OH)D levels above 20 ng/mL in 96.2% of those healthy young adults without inducing unacceptably high 25(OH)D concentration. This supplementation is safe and may be proposed without 25(OH)D testing.

A prospective, randomised, open-label trial was conducted to compare the efficacy and safety of a 10-day, high-dose versus a 3-month, continuous low-dose oral colecalciferol courses in a vitamin D deficient population. Fifty-nine vitamin D deficient inpatients (serum 25(OH)D ≤ 50 nmol/L) were enrolled. Participants were randomly assigned to a high-dose regimen of colecalciferol 50 000 IU daily for 10 days or a 3-month, continuous low-dose colecalciferol regimen of 3000 IU daily for 30 days, followed by 1000 IU daily for 60 days. Both groups received calcium citrate 500 mg daily. Twenty-six patients completed the study within 3 ± 1 months. The mean increases in serum 25(OH)D were similar in both the high- and low-dose groups (to 55 v 51 nmol/L, respectively; $P = 0.9$). There was no significant difference in the proportion of subjects who attained serum 25(OH)D concentrations > 50 nmol/L between the high- and low-dose groups (9/10 v 13/14, respectively; $P = 1.0$). Hypercalciuria (urine calcium > 7.5 mmol/day) occurred in three patients (two low-dose, one high-dose), while renal impairment worsened in one patient. No patient developed hypercalcaemia (corrected calcium > 2.6 mmol/L), vitamin D toxicity (25(OH)D > 200 nmol/L) or nephrolithiasis during the study. Both the 10-day, high-dose and the 3-month, low-dose colecalciferol regimens effectively increased serum 25(OH)D to within the normal range. The high-dose regimen may be an effective and cheap alternative for patients with vitamin D deficiency.

A longitudinal, retrospective nested cohort study aimed to compare the efficacy of weekly versus monthly supplementation with colecalciferol 20,000 IU in a group of people living with human immunodeficiency virus (PLWH) with vitamin D deficiency in Western Europe. Of 307 patients with vitamin D deficiency, 124 patients received vitamin D supplementation (weekly supplementation in 84 (67.7%)). 46.4% and 22.5% of patients achieved 25(OH)D levels ≥30 ng/mL after 12 months of weekly and monthly supplementation with colecalciferol 20,000 IU, respectively ($p=0.011$). Dosing interval as well as 25(OH)D baseline levels >15 ng/mL were associated with the normalisation of 25(OH)D. A higher rate of 25(OH)D level normalisation can be achieved via weekly supplementation. For several PLWH, even a weekly dose of colecalciferol 20,000 IU might not be adequate to maintain 25(OH)D levels >30 ng/mL without an initial "loading" dose. The response to supplementation is poorly predictable at an individual level.

Considering the frequency of vitamin D deficiency after Roux-en-Y gastric bypass (RYGB), most practitioners routinely prescribe vitamin D and calcium supplements after bariatric surgery. The current recommended doses are 400–800 IU of colecalciferol and 500–2000 mg of calcium per day.

In one case, it was reported that vitamin D and calcium supplements were not prescribed until several years after surgery, and the dose prescribed was insufficient to prevent vitamin D deficiency. Furthermore, the calcium dose at 1500 mg per day and 25- hydroxivitamin D dose at 16000 IU per week that was prescribed at the first medical intervention failed to control hypocalcaemia. An infusion of calcium gluconate was needed over seven days to elevate calcium levels, at which point oral regimens were then effective in controlling these deficiencies. This demonstrates the importance of the use of the high doses that are often

necessary to achieve normal vitamin D and calcium levels. Doses of 5000 IU per day have been found to be safe and necessary in many patients following Roux-en-Y gastric bypass. When malabsorption is suspected (in the case of extended surgical gastric by-passes) clinical studies have shown that doses as high as 50,000 IU of colecalciferol per day can be safely administered. In this case, high doses were required to maintain an adequate vitamin D status, so 16,000 IU of 25-hydroxivitamin D every 72 hours were maintained during follow-up and could not be reduced. Taking into account that 25-hydroxivitamin D is considered to have a biological potency 10 times higher than colecalciferol, the patient finally needed the equivalent of 53,000 IU of colecalciferol per day.

A double-blinded randomised controlled trial was conducted to examine effects of vitamin D supplementation on cardiovascular disease (CVD) risk factors in vitamin D-insufficient subjects. A 4-month interventional study with high-dose vitamin D (100,000 IU loading dose, followed by 20,000 IU/week) or placebo with measurements of blood pressure, lipids (total-, LDL- and HDL-cholesterol, triglycerides, apolipoproteins A1 and B), and glucose metabolism parameters (blood glucose, HbA1c, serum human receptors for advanced glycation end products (sRAGE), insulin, C-peptide and HOMA-IR) was conducted. A total of 422 subjects with mean serum 25(OH)D level 34 nmol/L were included, with 411 subjects completing the study. Serum 25(OH)D levels increased with 56 nmol/L and decreased with 4 nmol/L in the vitamin D and placebo group, respectively. The study found no statistically significant differences between the two groups in any of the measured CVD risk factors, except for a minor increase in sRAGE in the vitamin D group. Stratified analyses of subjects with low baseline serum 25(OH)D levels alone, or combined with blood pressure, lipid and HOMA-IR values above the median for the cohort, did not skew the results in favour of vitamin D supplementation. It was concluded that supplementation with vitamin D in subjects with baseline vitamin D insufficiency does not improve CVD risk factor profile.

In another study, a total of 208 vitamin D-deficient subjects (serum 25-hydroxyvitamin D3 (25- OHD3) level <50 nmol/l), aged 18-88 years, were treated with solubilised colecalciferol 50,000 IU/ml. They received either 25,000 IU every fortnight for 8 weeks (total dose 100,000 IU), 25,000 IU every week for 6 weeks (total dose 150,000 IU), or 25 000 IU every week for 8 weeks (total dose 200,000 IU). Most patients were severely vitamin D deficient: 76% had a serum 25-OHD3 level <30 nmol/l at baseline. Colecalciferol in a cumulative dose of 100,000, 150,000, and 200,000 IU increased mean serum 25-OHD3 level by 29 nmol/l (95% confidence interval (CI): 23-35 nmol/l), 43 nmol/l (95% CI: 36-50 nmol/l), and 69 nmol/l (95% CI: 64-75 nmol/l) respectively. The change in 25-OHD3 (Delta25-OHD3) was related to the dose per kilogram body weight (R2=0.38, P<0.0001), and is described by the equation: Delta25- OHD3=0.025 x (dose per kg body weight). The colecalciferol loading dose required to reach the serum 25-OHD3 target level of 75 nmol/l can be calculated as follows: dose (IU) = 40 x (75-serum 25-OHD3) x body weight. Vitamin D deficiency (<32 ng/mL) is a reversible cause of statin-intolerance, usually requiring vitamin D3 (50,000-100,000 IU/week) to normalise serum D, allowing reinstitution of statins.

A study prospectively assessed the safety-efficacy of vitamin D3 therapy. In 282 statin-intolerant hyper-cholesterolemic patients for 6 months and in 112 of the 282 patients for 12 months, with low-entry serum vitamin D (<32 ng/mL), authors assessed the safety-efficacy of vitamin D3 therapy (50,000-100,000 IU/week). On mean (66,600 IU) and median (50,000 IU) of vitamin D3/week in 282 patients at 6 months, serum vitamin D rose from pre-treatment (21-median) to 46 ng/mL (P < 0.0001) and became high (>100 ng/mL) but not toxic (>150 ng/mL) in 4 patients (1.4%). Median serum calcium was unchanged from entry (9.60 mg/dL) to 9.60 at 6 months (P =0.36), with no trend of change (P = 0.16). Median eGFR was unchanged from entry (84 mL/min/1.73) to 83 at 6 months (P = 0.57), with no

trend of change (P = 0.59). On vitamin D3 71,700 (mean) and 50,000 IU/week (median) at 12 months in 112 patients, serum vitamin D rose from pre-treatment (21-median) to 51 ng/mL (P < 0.0001) and became high (>100 but <150 ng/mL) in 1 (0.9%) at 12 months. Median serum calcium was unchanged from entry (9.60 mg/dL) to 9.60 mg/dL and 9.60 mg/dL at 6 months and 12 months, respectively; P > 0.3. eGFR did not change from 79 mL/min/1.73 at entry to 74 mL/min/1.73 and 77 mL/min/1.73 at 6 months and 12 months, P > 0.3. There was no trend in the change in serum calcium (P > 0.5 for 6 months and 12 months), and no change of eGFR for 6 months and 12 months, P > 0.15. Vitamin D3 therapy (50,000-100,000 IU/week) was safe and effective when given for 12 months to reverse statin intolerance in patients with vitamin D deficiency. Serum vitamin D rarely exceeded 100 ng/mL, never reached toxic levels, and there was no significant change in serum calcium or eGFR.

Another study was conducted to determine an adapted supplementation of vitamin D deficient able to quickly and safely increase the vitamin D status of healthy adults with low 25(OH)D. One hundred and fifty (150) subjects were randomised into three groups, each to receive, orally, a loading dose of 50,000, 100,000 or 200,000 IU of vitamin D3 at Week 0, followed by 25,000, 50,000 or 100,000 IU at Week 4 and Week 8. Whereas 25(OH)D baseline values were not different between groups (p = 0.42), a significant increase was observed at Week 12 (p < 0.0001) with a mean change from baseline of 7.72 ± 5.08, 13.3 ± 5.88 and 20.12 ± 7.79 ng/mL. A plateau was reached after eight weeks. This study demonstrated a linear dose response relationship with an increase in 25(OH)D levels proportional to the dose administered. In conclusion, a loading dose of 200,000 IU vitamin D3 followed by a monthly dose of 100,000 IU is the best dosing schedule to quickly and safely correct the vitamin D status.

A one-year, double blind placebo-controlled intervention trial performed. 421 subjects, 21 - 70 years old, were included and 312 completed the study. The subjects were randomised to vitamin D3 40,000 IU per week (DD group), vitamin D3 20,000 IU per week (DP group), or placebo (PP group). All subjects were given 500 mg calcium daily. At baseline the mean serum 25(OH) D levels were 58 nmol/L (all subjects) and increased to 141 and 100 nmol/L in the DD and DP groups, respectively. At the end of the study serum 25(OH) D levels were 140.9 ± 34.7 nmol/L, 99.7 ± 20.3 nmol/L, and 57.9 ± 20.4 nmol/L in the DD, DP and PP groups respectively. There was a highly significant positive correlation between baseline and 12 months' serum 25(OH) D in both the DD and DP groups (r = 0.40 and r = 0.69, respectively (P < 0.001)), and a significant negative correlation between baseline and delta serum 25(OH) D (r = - 0.57 and r = - 0.49, respectively (P < 0.001)). After one year, no significant differences were found between the three groups regarding change in BMD, serum OPG or RANKL. Supplementation with high doses of vitamin D for one year does not appear to have a negative effect on BMD in healthy subjects.

As adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency
A study aimed to investigate vitamin D status and supplementation in ambulatory patients. Nine hundred seventy-five women and 188 men were evaluated for bone status from January 2008 to August 2008 within an observational study; 104 patients (n = 70 osteoporosis) received follow-up after 3 months. Dosage of vitamin D supplementation was documented and serum 25(OH)D and PTH determined. In all patients (age, 60.4 ± 14.1 years), distribution of 25(OH)D was 56.3 ± 22.3 nmol/L (normal range, 52-182 nmol/L) and PTH 53.8 ± 67.5 ng/L (normal range, 11-43 ng/L). The proportion of patients with 25(OH)D < 25, 25 to <50, 50 to <75, ≥75 nmol/L was 7.5%, 33.3%, 38.9% and 20.2% in the total group and 20.1%, 38.5%, 30.8%, 10.6% at baseline in the follow-up group, respectively. After 3 months, 3.9% had still 25(OH)D < 25 nmol/L; only 12.5% achieved 25(OH)D ≥ 75 nmol/L. In osteoporosis patients, 25(OH)D increased more in those taking ≥1,500 (median, 3,000) IU

vitamin D per day (33.1 ± 14.7 nmol/L) compared with ≤1,000 (median, 800) IU/day (10.6 ± 20.0 nmol/L) ($p < 0.0008$). PTH decreased more in patients taking ≥1,500 IU/day (-13.2 ± 15.2 ng/L) compared with ≤1,000 IU/day (-7.6 ± 19.2 ng/L; $p = 0.29$). 25(OH)D was negatively correlated to PTH ($r = -0.49$, $p < 0.0001$). An increase of 25(OH)D ≥ 75 nmol/L resulted in normalised PTH. Supplementation with higher vitamin D dosages (2,000- 3,000 IU/day) is required to achieve a relevant increase of 25(OH)D and normalisation of PTH.

Another study was conducted to evaluate the efficacy and safety of 15,000 IU/week (equivalent to 2000 IU/day) vitamin D administrated in 52 postmenopausal women with osteopenia or osteoporosis. Patients were divided into two groups. The treated group was supplemented by calcium 0.5 g/d and 25-hydroxycholecalciferol 15,000 IU/week and the control group was supplemented by calcium and placebo for two months. Plasma calcium concentration did not change in the vitamin D treated group while it decreased ($p < 0.001$) in the control group. Neither calciuria nor fractional excretion of calcium changed during the treatment period. Plasma inorganic phosphate concentration did not change in any group, but urinary inorganic phosphate excretion increased in the vitamin D treated group ($p < 0.001$). The starting 25-hydroxycholecalciferol plasma concentrations were almost at the deficiency range in both groups. The 25-hydroxycholecalciferol plasma concentration increased substantially ($p<0.001$) in the treated group, but it remained at the starting level in control group during the treatment period. Similar plasma concentration increase ($p < 0.001$) was apparent also in 1.25- dihydroxycholecalciferol. Plasma intact parathormone concentration did not change in the vitamin D treated patients, while it increased ($p < 0.01$) in the control group. None of the vitamin D treated women suffered from hypercalcemia and mild hypercalciuria was observed in one patient. In conclusion, the study presents evidence on the effectiveness and safety of 15,000 IU/week 25-hydroxycholecalciferol dosage schedule.

The international Multiple Outcomes of Raloxifene Evaluation study, a large prospective intervention trial in postmenopausal women with osteoporosis, offered the opportunity to compare vitamin D status and parathyroid function throughout many countries over the world. For this study, baseline data were available from 7564 postmenopausal women from 25 countries on 5 continents. A low serum 25OHD (<25 nmol/L) was observed in 4.1% of all women. Serum 25OHD was between 25-50 nmol/L in 24.3% of the women. Serum PTH correlated negatively with serum 25OHD ($r = -0.25$; $P < 0.001$). When serum 25OHD was less than 25, 25-50, or more than 50 nmol/L, respectively, mean serum PTH levels were 4.8, 4.1, and 3.5 pmol/L, respectively (by ANOVA, $P < 0.001$). Similarly, mean alkaline phosphatase levels were 83.7, 79.1, and 75.7 U/L ($P < 0.001$), respectively, with increasing serum 25OHD. The effect of serum 25OHD on BMD was only significant for the BMD of the trochanter where a serum 25OHD level less than 25 nmol/L was associated with a 4% lower BMD. After 6 months of treatment with vitamin D3 (400-600 IU/day) and calcium (500 mg/day), serum 25OHD increased from 70.8 ± 29.8 to 92.3 ± 28.6 nmol/L. Serum PTH decreased significantly after 6 months of treatment, and this decrease depended on baseline serum 25OHD. When baseline serum 25OHD was less than 25, 25-50, or more than 50 nmol/L, respectively, serum PTH decreased by 0.8, 0.5, or 0.2 pmol/L, respectively ($P < 0.001$). Treatment with vitamin D3 and calcium increased serum 25OHD and decreased serum PTH significantly; the effect was greater for lower baseline serum 25OHD.

A meta-analysis of studies assessed the role of vitamin D in corticosteroid-induced osteoporosis. All randomised controlled trials, lasting at least 6 months comprising of patients receiving corticosteroids and comparing vitamin D supplementation 1) no therapy or calcium alone 2) bisphosphonate, calcitonin or fluoride in the management of corticosteroid-induced osteoporosis were included in the analysis. Study found a moderate beneficial effect of vitamin D plus calcium versus no therapy or calcium alone (9 trials) (effect size 0.60; 95%

confidence interval [95% CI] 0.34, 0.85; P < 0.0001). In comparisons of vitamin D with other osteoporosis therapies, bisphosphonates were more effective than vitamin D (6 trials) (effect size 0.57; 95% CI 0.09, 1.05). Calcitonin was similar in efficacy to vitamin D (4 trials) (effect size 0.03; 95% CI -0.39, 0.45). Fluoride was more effective than vitamin D, but there were only 2 trials. Vitamin D plus calcium is superior to no therapy or calcium alone in the management of corticosteroid-induced osteoporosis. Vitamin D is less effective than some osteoporosis therapies. It was concluded that treatment with vitamin D plus calcium, as a minimum, should be recommended to patients receiving long-term corticosteroids.

Conclusion on efficacy
It is accepted that the use of colecalceferol for the prevention and treatment of vitamin D deficiency is well established. The detailed references summarised above from published scientific literature have used a variety of dose strengths in the clinical studies. Clinical symptoms of vitamin D manifest as osteomalacia in adults. For indications of supportive treatment in osteoporosis, daily doses of approximately 800 IU of vitamin D3 daily have been systematically used in most clinical studies. Similar doses are well established in the prevention of vitamin D deficiency in adolescents and adults with identified risk.

Higher doses (up to 4000 IU daily in adults and adolescents) may be necessary in the treatment of vitamin D deficiency, defined as serum 25-hydroxycalciferol (25OHD) <25 nmol/l. In these cases, the dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment. The maximum recommended daily doses should be in accordance with EFSA tolerable upper intake levels.

The applicant has provided a reasonable discussion and explanation regarding the bridging data linking the proposed formulation to the formulation used in the publications.

IV.5 Clinical safety
No new safety data were supplied or required for these bibliographic applications. The safety profile of colecalciferol is well-known and has been adequately summarised by the applicant in the clinical overview. No new or unexpected safety issues arose from the submitted safety data.

A summary of the clinical safety of colecalciferol as presented by the applicant is given below.

Adverse events
Numerous clinical studies have investigated the safety profile of colecalciferol. During a 3-month randomised open-label clinical trial, no serious adverse events were reported after the oral administration of 500 and 1000 IU/day oral colecalciferol, in postmenopausal women (n=92, aged 40-73 years). However, minor gastritis and abdominal discomfort were reported in 12 subjects, but this did not result in the withdrawal of supplementation. In one study the safety of high doses of vitamin D supplementation and concomitant use of calcium in vitamin D deficient subjects was investigated. In this study, 52 healthy subjects (mean age of 48 ± 15 years, 17M and 35F) were supplemented with colecalciferol 9572 IU/day and elemental calcium 1 gm/day. After 2 months of therapy: those who attained vitamin D sufficiency (n=12) were supplemented with colecalciferol 3000 IU/day; and those who were still vitamin D insufficient were supplemented with colecalciferol 5286 IU/day along with 1 gm elemental calcium. All subjects were then reassessed after three months. The mean ± SD of serum calcium, phosphorous, alkaline phosphatase were in the normal range at baseline, 2 and 5 months of supplementation. In addition, no participants presented with hypercalcaemia

including the subjects receiving vitamin D supplementation alongside an elemental calcium supplement of 1gm/day. The findings of this study demonstrate that high doses of vitamin D supplementation did not produce hypercalcaemia despite concomitant use of elemental calcium.

Similarly, a study reported that 1800 IU/day colecalciferol treatment caused no clinical or metabolic side-effects. The study demonstrated that high doses of vitamin D supplementation (1800IU/day) are generally safe as a prophylactic treatment of vitamin D deficiency in the elderly. Moreover, in the study conducted by), healthy men and women (n=61, aged 18-56 years) were randomised to either 1000 or 4000IU/day vitamin D3 for 2-5 months. During the study there were no significant changes in serum calcium and urinary calcium excretion at either dosage. The study demonstrated that prolonged daily supplementation with either 1000IU or 4000IU Colecalciferol is safe in increasing and maintaining serum 25(OH)D3 levels within the physiological range in adults. Furthermore, a later similar study conducted by, but this time using doses of 600 and 4000 IU, concluded that the higher dose (4000 IU) is physiologic and safe. Moreover, this study also measured patient wellbeing. The study found that the feelings of wellbeing were sustained for one year at the highest dose, longer than the lower treatment. Furthermore, the authors argue that this trial provided a new perspective on the safety of vitamin D at these higher doses, as in the earlier study. Neither of the dosing levels studied affected serum calcium levels. Moreover, the researchers observed that the safety aspects of the higher dose are also supported by the wellbeing of the patients and was not made worse by the consumption of the higher dose; instead, it improved.

In another placebo-controlled, randomised, double-blind study, elderly subjects (age: ≥70 years) with hypovitaminosis D were given either oral Colecalciferol 2,000 IU (n=17) or placebo daily (n=17) for 6 months. In the treatment group three participants had adverse events resulting in their withdrawal from the study, which included ankle swelling, bradycardia and myocardial infarction. One patient also complained of an episode of diarrhoea but remained in the study. However, all adverse events reported were considered unrelated to vitamin D supplementation. In addition to this, vitamin D supplementation did not alter serum or urinary calcium levels. To conclude this supports that 2000IU/day Colecalciferol is safe in treating hypovitaminosis D in elderly patients. Colecalciferol is naturally synthesised in the human skin through the action of sun rays. Prolonged sunlight exposure does not lead to excess production of vitamin D as a regulation mechanism exists to destroy excess pre-vitamin D3 in the skin. However, high doses of vitamin D supplements can be toxic (resulting in hypercalcaemia and renal failure). It is stated that this is more likely to occur if high dose formulations (used as initial treatment loading doses) are taken over a prolonged period of time, or if alfacalcidol or calcitriol are given in error. Therefore, calcium levels should be monitored in the blood during Colecalciferol treatment. There is also a small risk of hypercalcaemia developing in the presence of undiagnosed sarcoidosis or primary hyperparathyroidism. It is reported that Vitamin D over-dosage can cause hypercalcaemia and other associated side-effects like anorexia, nausea, vomiting, diarrhoea, constipation, lassitude, vertigo, polyuria, nocturia, somnolence, thirst, sweating, headache and weight loss.

According to a Vitamin D expert review, there is little evidence that long-term supplementation between 10-25 μg (400-1000 IU) per day would be harmful and, indeed, a meta-analysis of randomised trials in elderly people with a low vitamin D status found that daily supplementation of 10-20 μg (400-800 IU) led to a 7% lower risk of all-cause mortality. However, there is a lack of evidence about the possible risks of chronically raising levels of vitamin D in healthy people through supplementation. Studies like NHANES III suggest that high levels of vitamin D beyond the threshold of 75nmol/L could be associated with adverse effects, including increased all-cause mortality and incidence of cardiovascular diseases.

The safety of ergocalciferol (vitamin D2) and colecalciferol was also evaluated in a trial where both were administered either at 1600 IU daily or 50,000 IU monthly in older adults for one year. The overall results demonstrated that colecalciferol was significantly more effective than ergocalciferol in increasing serum calcidiol levels. One year of either ergocalciferol or colecalciferol dosing (1,600 IU daily or 50,000 IU monthly) did not produce toxicity, and calcidiol levels of less than 30 ng/ml persisted in approximately 20% of individuals despite good compliance. A substantial difference between each individual's response to administered ergocalciferol and colecalciferol was observed.

Pregnancy & Lactation
There is limited data on the use of colecalciferol in pregnant women. The recommended daily intake for pregnant women is 400 IU, however, in women who are considered to be Vitamin D3 deficient a higher dose may be required (up to 2000 IU/day- 10 drops with the oral drops presentation).

The efficacy and safety of prenatal vitamin D3 supplementation has been investigated in a randomised controlled clinical trial. Pregnant Arab women, who were vitamin D deficient, were randomised at 12–16 weeks of gestation to 400, 2000, and 4000 IU/day vitamin D3, which were continued to delivery. Maternal and cord blood 25(OH)D3 levels at delivery were measured and recorded. The data indicated that mean serum 25(OH)D3 concentrations at delivery and in cord blood were significantly higher in the 2000 and 4000 IU/d groups than the 400 IU/d group and was highest in the 4000 IU/d group. Serum 25(OH)D3 concentrations greater than 32 ng/mL and 20 ng/mL was highest in mothers and infants treated with 4000 IU/day. This finding indicates that a dose of 4000 IU/d is most effective in optimising serum 25(OH)D3 concentrations in mothers and their infants. Throughout the study period, there were no adverse events attributable to vitamin D3 supplementation. There was no evidence of hypercalcaemia because total serum calcium concentrations tended to fall during pregnancy in all groups.

During pregnancy women should follow the advice of their medical practitioner as their requirements may vary depending on the severity of their disease and their response to treatment Vitamin D3 and its metabolites are excreted in breast milk.

Vitamin D3 can be prescribed while the patient is breast-feeding if necessary. This supplementation does not replace the administration of Vitamin D3 in the neonate.

There is no data regarding treatment with vitamin D3 and its effects on fertility.

The effect of colecalciferol in the elderly
A three-year double-blind randomised clinical trial was conducted to establish whether vitamin D doses up to 10000 IU/day are safe and well-tolerated. Healthy adults (n=373) aged 55-70 with serum 25-hydroxyvitamin D 30-125 nmol/L were enrolled in the study. Participants were randomised 1:1:1 to vitamin D3 400, 4000 or 10000 IU/day. The safety profile of vitamin D supplementation was similar for doses of 400, 4000 and 10000 IU/day. Hypercalciuria was common and occurred more frequently with higher doses. Hypercalcemia occurred more frequently with higher doses but was rare, mild, and transient. The authors concluded that in healthy adults who are not vitamin D deficient, daily vitamin D supplementation with doses of 400,4000, and 10000 IU for up to three years is generally safe and well tolerated.

An open-label feasibility study was conducted to determine if 4000 IU per day of vitamin D3

is safe for frail older adults. Forty older adults (≥ 75 years) with frail or pre-frail characteristics were treated with 4000 IU of vitamin D3 and 1200 mcg of calcium carbonate daily for four months. The dosing strategy did not lead to an adverse event, nor to the development of hypercalcemia. No participant, regardless of baseline vitamin D or frailty status, experienced an adverse outcome. Vitamin D supplementation using 4000 IU/daily was considered safe and had a modest beneficial effect on physical performance for frail individuals and those with insufficient vitamin D levels.

A randomised placebo-controlled trial was conducted in 305 community-dwelling people aged 65 years or older, with the aim to assess the effects of daily supplementation with vitamin D3 4000 IU (100 μg),2000 IU (50 μg) or placebo for one year on biochemical markers of vitamin D status in preparation for a large trial for prevention of fractures and other outcomes. After accounting for average 70% compliance in long-term trials, doses of 4000 IU vitamin D3 daily may be required to achieve plasma 25(OH)D levels associated with lowest disease risk in observational studies. Supplementation with vitamin D had no significant effects on cardiovascular risk factors or on measure of physical function.

To investigate the safety of a monthly high-dose of vitamin D3 supplementation, data were collected in a randomised, double blind, placebo-controlled trial of 5108 adults aged 50-84 years old. Participants were given monthly doses of 100,000 IU vitamin D3 or placebo, for a median of 3.3 years (range 2.5-4.2 years) taken for up to 4years. In total, 419 (16.5%) participants taking vitamin D and 399 (15.8%) taking placebo reported ≥1adverse event. Compared to placebo, the hazard ratio (HR) of reporting first adverse event in the vitamin D group was 1.03 (95% CI: 0.90, 1.18; p = 0.63). All regression results were adjusted for age, sex, and ethnicity. There was no difference between study arms in terms of participants' allocation perception (p = 0.52). The study concluded that monthly supplementation of 100,000 IU vitamin D3 for a median of 3.3 years did not affect participant-reported adverse events.

Over a median of 3.3 y, monthly supplementation with 100,000 IU vitamin D3 did not affect the incidence rate of kidney stone events, or hypercalcemia.

A randomised controlled trial of vitamin D supplementation in older people to optimize bone health was conducted wherein a total of 379 adults aged ≥70 y (48% women; mean age: 75 year) were randomly allocated to one of three doses of vitamin D3 [12,000 IU, 24,000 IU, or 48,000 IU] given once a month. The mean ± SD baseline plasma 25-hydroxyvitamin D [25(OH)D] concentration was 40.0 ± 20.1 nmol/L, which increased after 12 months to a mean 25(OH)D of 55.9, 64.6, or 79.0 nmol/L for participants receiving a monthly dose of 12,000, 24,000, or 48,000 IU, respectively (P < 0.01 for difference). The treatment was safe and effective in increasing plasma 25(OH)D concentrations, with no dose-related adverse events.

Daily oral intake of vitamin D3 ranging from 5000 IU/d to 60,000IU/d for several years was well tolerated and safe in patients as per the hospital data record (n = 4700; 18 to 90 years old; 49.9% were black, 47.3% were white, and 2.8% were other races). The mean 25OHD blood levels in the patients took around 12 months to plateau on 5000 IU/d and 10,000 IU/d. 25OHD blood levels were not associated with hypercalcemia, nephrolithiasis, or any other adverse health effects in the study population. The study concluded that long-term supplementation with vitamin D3 in doses ranging from 5000 to 50,000 IUs/day appeared to be safe.

The above-mentioned data clearly suggests that the proposed product in the proposed dosage regimen will be safe and well tolerated in the geriatric population.

The effect colecalciferol in children and adolescents (under 18 years of age)
The proposed products have not been recommended for use in children and adolescents; hence data on safety of vitamin D3 in children have not been presented.

Overdose
Overdose of colecalciferol leads to increased serum and urinary phosphorus levels, as well as hypercalcaemic syndrome and consequently calcium deposits in the tissues and above all in the kidneys (nephrolithiasis, nephrocalcinosis) and the vessels.

Chronic overdosage may lead to vascular and organ calcification, as a result of hypercalcaemia. The symptoms of intoxication are little characteristic and manifest as nausea, vomiting, initially also diarrhoea, later constipation, loss of appetite, weariness, headache, muscle pain, joint pain, muscle weakness, persistent sleepiness, azotaemia, polydipsia and polyuria and, in the final stage, dehydration. Typical biochemical findings include hypercalcaemia, hypercalciuria, as well as increased serum 25 hydroxy colecalciferol concentrations. Hypercalcaemia is responsible for producing most of the symptoms of vitamin D toxicity.

Early symptoms of vitamin D toxicity include gastrointestinal disorders such as anorexia, diarrhoea, constipation, nausea, and vomiting. Bone pain, drowsiness, continuous headaches, irregular heartbeat, loss of appetite, muscle and joint pain are other symptoms that are likely to appear within a few days or weeks; other symptoms include frequent urination, especially at night, excessive thirst, weakness, nervousness and itching; kidney stones.

IV.6 Risk Management Plan (RMP)
The Applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The clinical overview contains an adequate review of published clinical data.

Choli-D3 10,000 IU and 50,000 IU Capsules, soft contain the widely used and well-known active substance, colecalciferol, which has a long history of established favourable risk-benefit profile.

The applicant has provided a reasonable discussion and explanation to bridge the proposed formulations to those reported in the published literature.

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the applications, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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

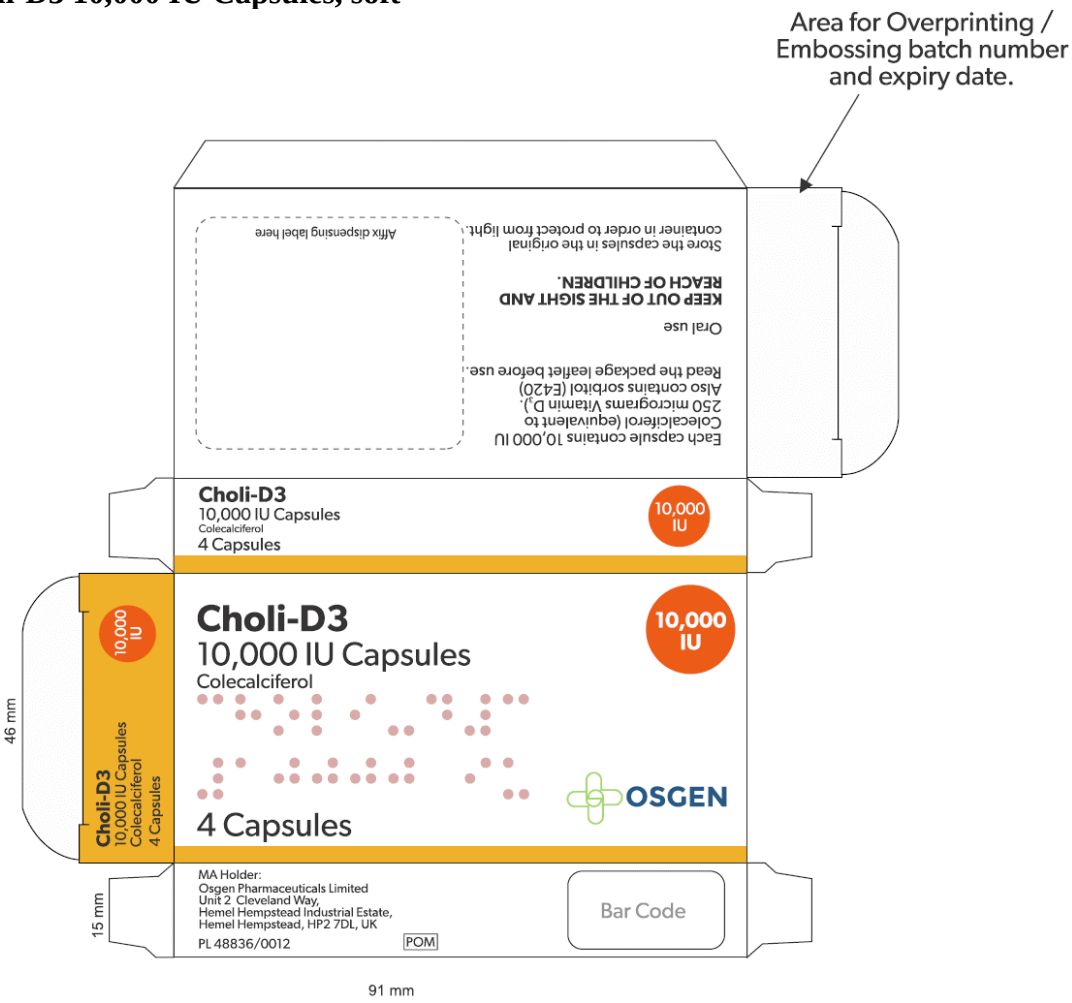
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with colecalciferol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

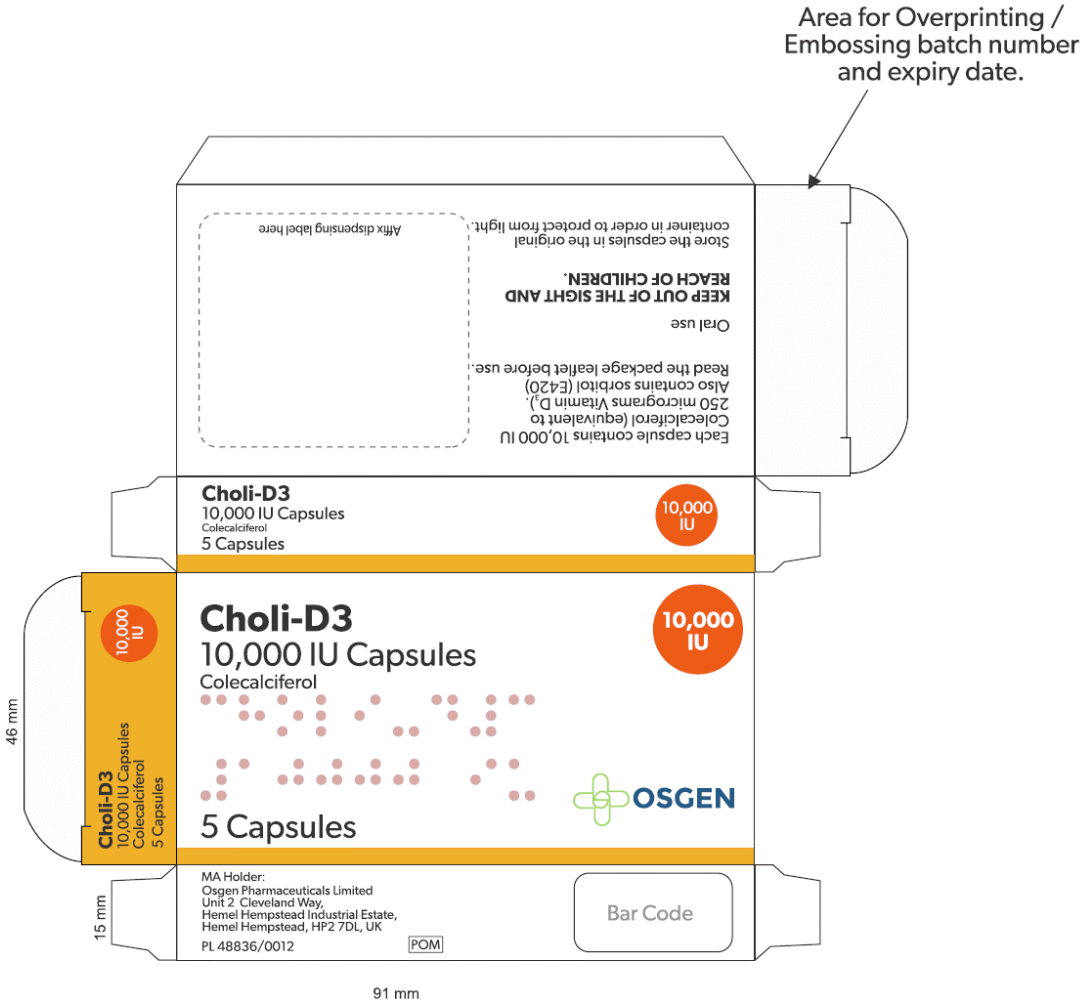
The Summaries of Product Characteristics (SmPCs), PIL and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.

Choli-D3 10,000 IU Capsules, soft




Area for Overprinting / Embossing batch number and expiry date.
Each capsule contains 10,000 IU Colecalciferol (equivalent to 250 micrograms Vitamin D3). Also contains sorbitol (E420) Read the package leaflet before use.
Oral use
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Store the capsules in the original container in order to protect from light.
Affix dispensing label here
Choli-D3
10,000 IU Capsules
Colecalciferol
5 Capsules
10,000 IU
Choli-D3
10,000 IU Capsules
Colecalciferol
5 Capsules
10,000 IU
OSGEN
MA Holder:
Osgen Pharmaceuticals Limited
Unit 2 Cleveland Way,
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Hemel Hempstead, HP2 7DL, UK
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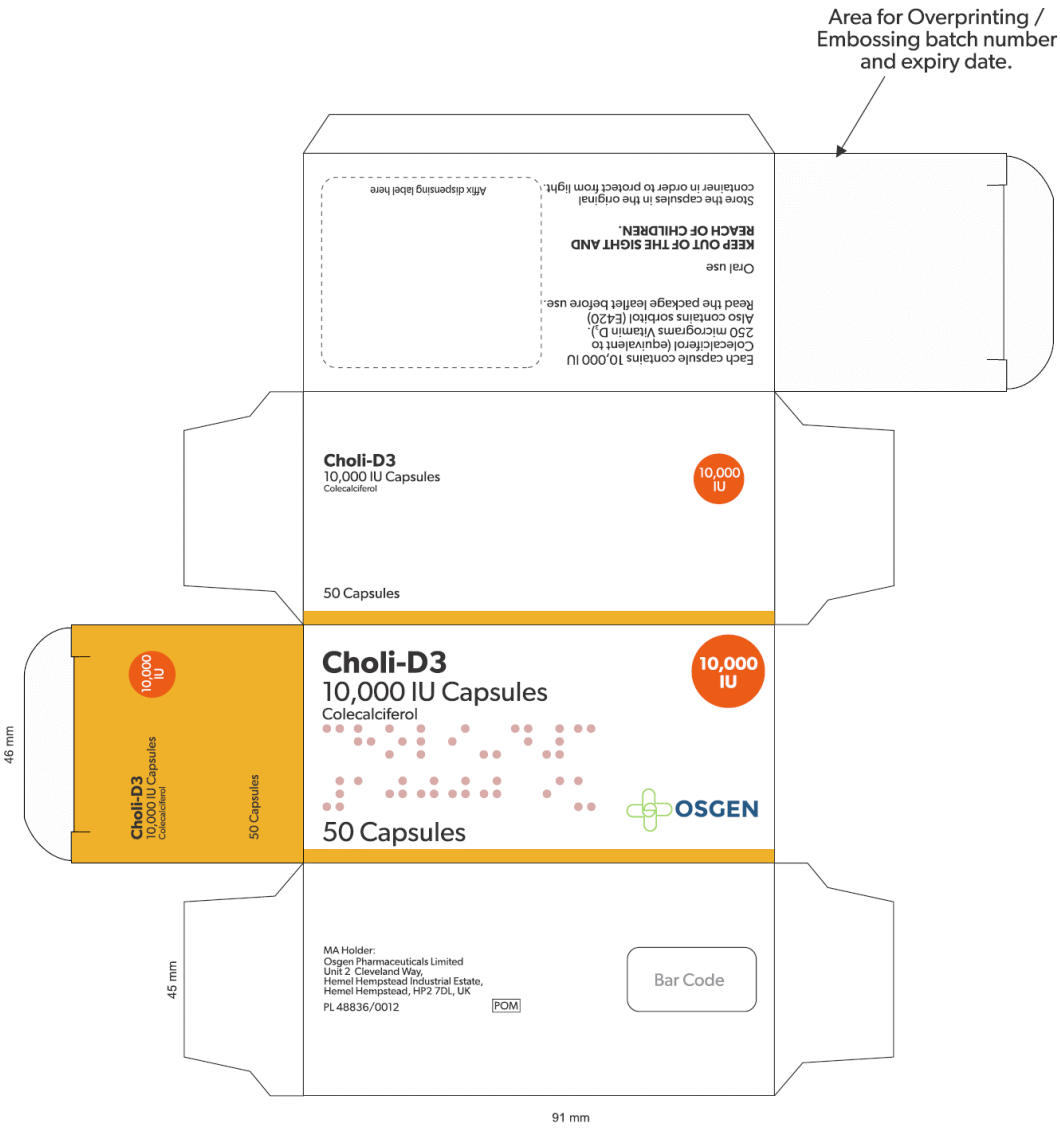
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Choli-D3
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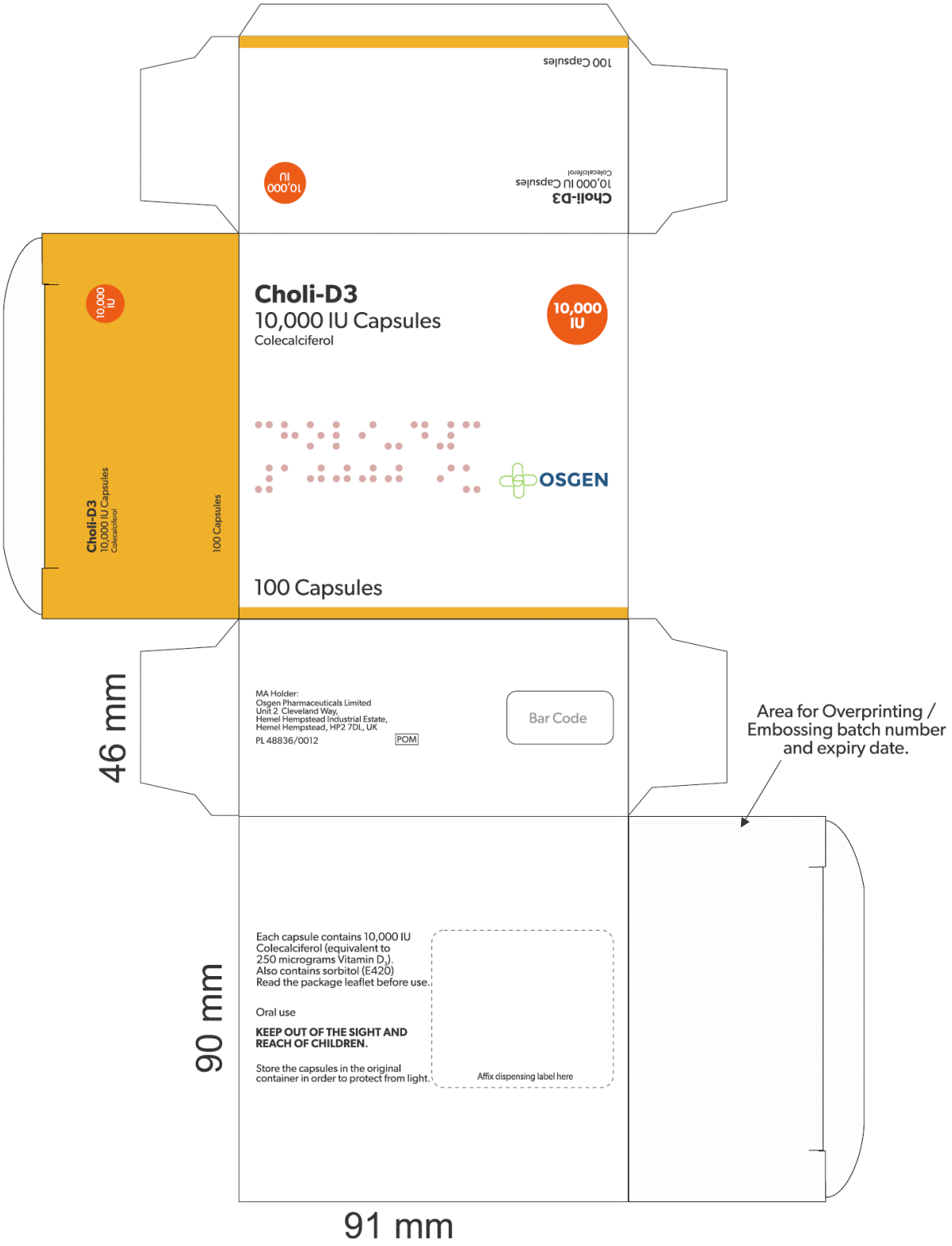
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Unit 2 Cleveland Way,
Hemel Hempstead Industrial Estate,
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Bar Code
Area for Overprinting / Embossing batch number and expiry date.
46 mm
Each capsule contains 10,000 IU Colecalciferol (equivalent to 250 micrograms Vitamin D3).
Also contains sorbitol (E420)
Read the package leaflet before use.
Oral use
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Store the capsules in the original container in order to protect from light.
Affix dispensing label here
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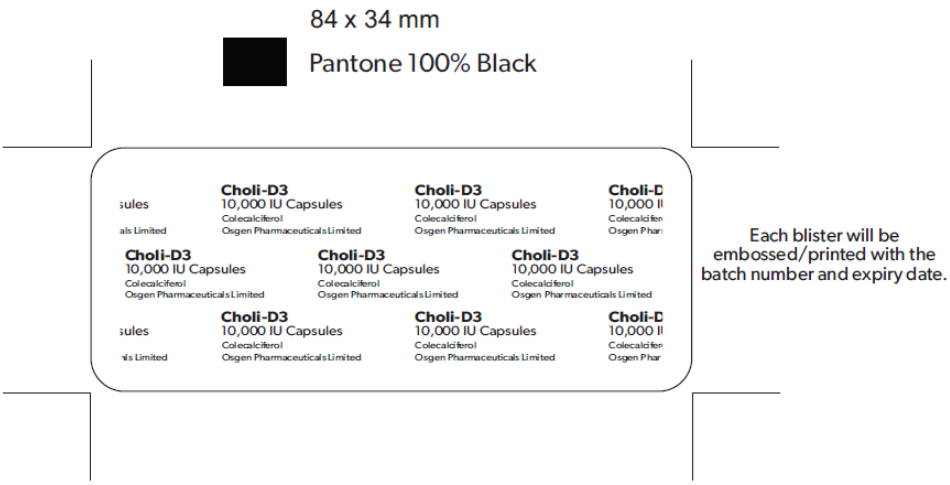
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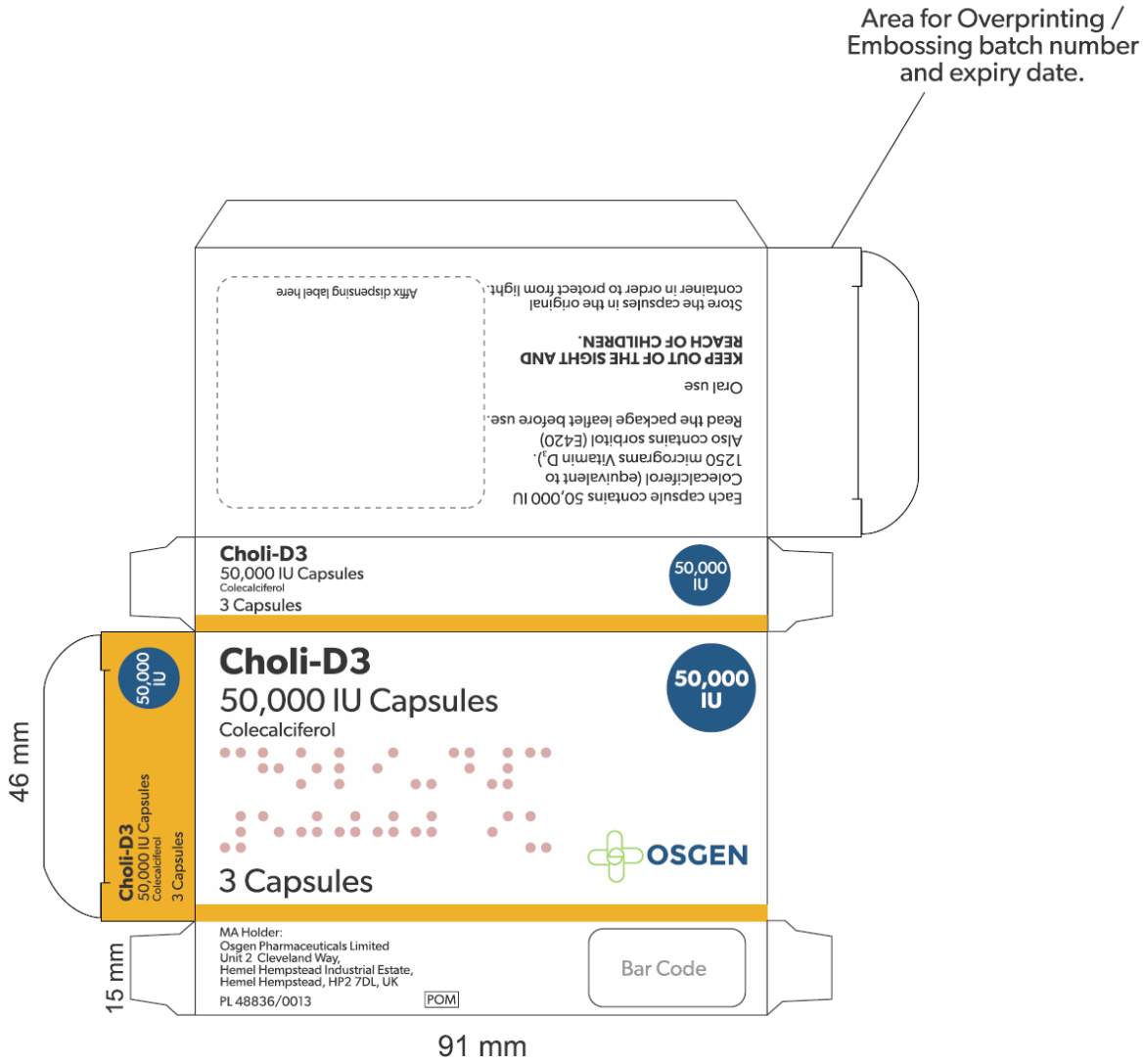
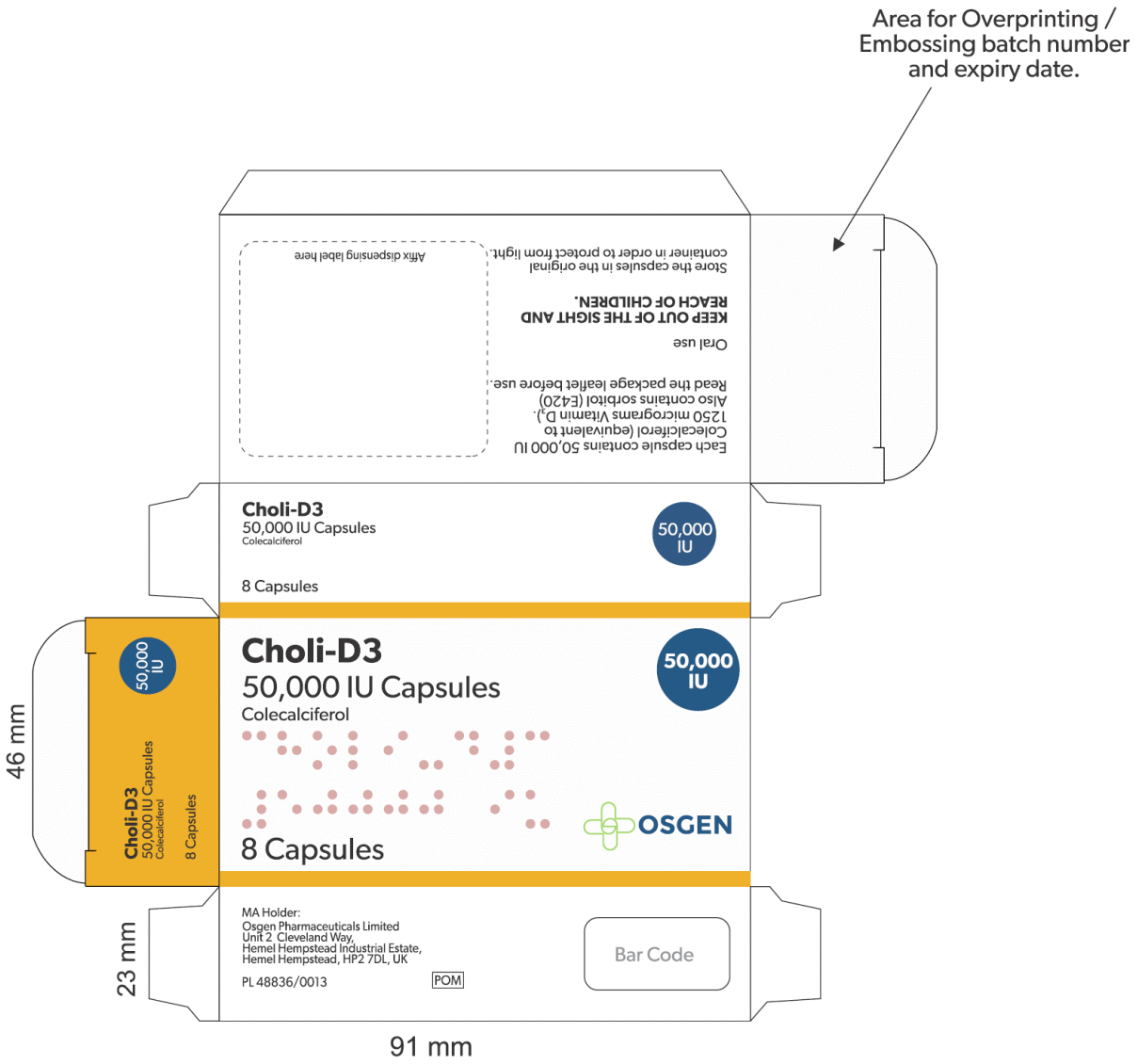
Choli-D3
10,000 IU Capsules
Colecalciferol
Osgen Pharmaceuticals Limited
Each blister will be embossed/printed with the batch number and expiry date.

Choli-D3 50, 000 IU Capsules, soft




Area for Overprinting / Embossing batch number and expiry date.
Affix dispensing label here
Store the capsules in the original container in order to protect from light.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Oral use
Read the package leaflet before use.
Also contains sorbitol (E420)
1250 micrograms Vitamin D3.
Cholecalciferol (equivalent to
Each capsule contains 50,000 IU
Choli-D3
50,000 IU Capsules
Colecalciferol
8 Capsules
50,000 IU
Choli-D3
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Colecalciferol
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Choli-D3
50,000 IU Capsules
Colecalciferol
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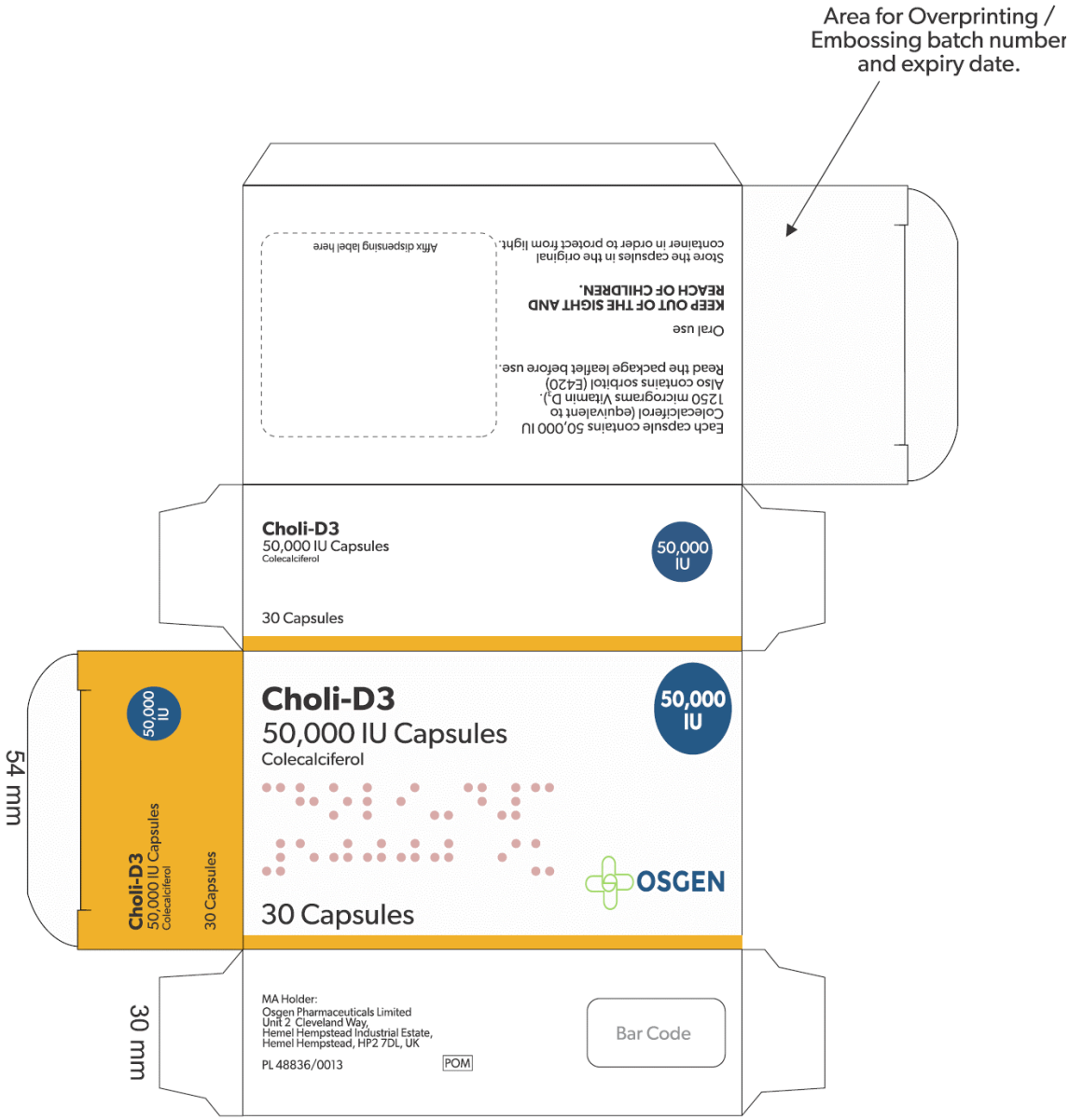
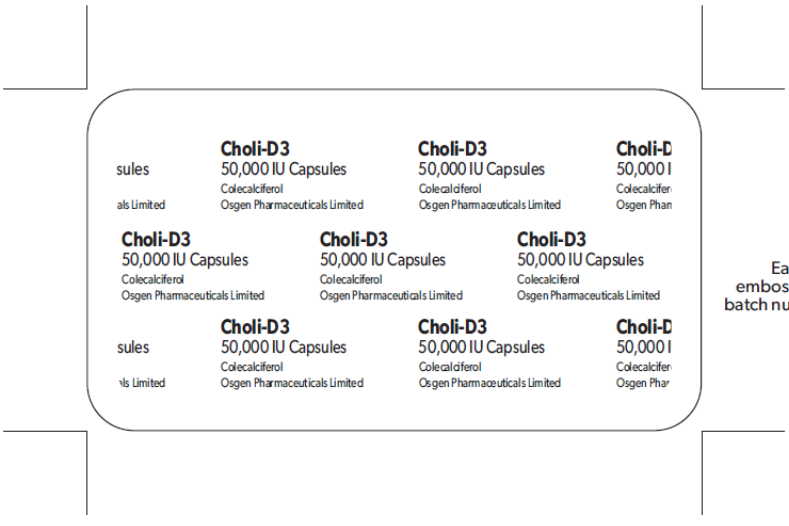


90 x 50 mm-

Pantone 100% Black



Each blister will be embossed/printed with the batch number and expiry date.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisations are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**