Public Assessment Report

Decentralised Procedure

Aviticol 20 000 IU Capsules

Cholecalciferol 20 000 IU Capsules

UK/H/5473/001/DC

PL 41344/0001

Colonis Pharma Limited

LAY SUMMARY

This is a summary of the public assessment report (PAR) for Aviticol 20 000 IU Capsules/Cholecalciferol 20 000 IU Capsules (PL 41344/0001). It explains how Aviticol 20 000 IU Capsules/Cholecalciferol 20 000 IU Capsules 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 Aviticol 20 000 IU Capsules/Cholecalciferol 20 000 IU Capsules.

Aviticol 20 000 IU Capsules/Cholecalciferol 20 000 IU Capsules are identical to each other apart from the difference in product name and will be collectively referred to as Cholecalciferol 20 000 IU Capsules in the remainder of this report.

For practical information about using Cholecalciferol 20 000 IU Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Cholecalciferol 20 000 IU Capsules and what are they used for?
Cholecalciferol 20 000 IU Capsules is a medicine with 'well-established use'. This means that the medicinal use of the active substance, cholecalciferol, has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Cholecalciferol is a source of vitamin D used in the prevention and treatment of vitamin D deficiency conditions.

How do Cholecalciferol 20 000 IU Capsules work?
Each capsule contains the equivalent of 500 micrograms vitamin D_3. Vitamin D_3 is involved in bone formation and is usually obtained through a normal diet or produced in the skin after exposure to sunlight. Deficiency of vitamin D_3 may occur when a person's diet or lifestyle does not provide them with enough vitamin D_3 or when their body requires extra vitamin D_3 (for instance when they are pregnant).

How are Cholecalciferol 20 000 IU Capsules used?
The capsules should be swallowed whole with a glass of water, preferably with the main meal of the day.

Adults using the capsules for the treatment of vitamin D deficiency should take two capsules per week for 7 weeks, followed by a maintenance regime of 2-3 capsules every 4 weeks, as directed by their doctor.

Adults using the capsules for the prevention of vitamin D deficiency should take one capsule every 4 weeks. Higher doses may be required in certain situations, as directed by a doctor.

Children aged 12-18 years using the capsules for the treatment of vitamin D deficiency should take one capsule every 2 weeks for 6 weeks

Children aged 12-18 years using the capsules for the prevention of vitamin D deficiency should take one capsule every 6 weeks.

The medicine can only be obtained from a pharmacy with a prescription.

What benefits of Cholecalciferol 20 000 IU Capsules have been shown in studies?
As cholecalciferol is a well-known substance and its use in the treatment and prevention of vitamin D deficiency is well-established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of cholecalciferol in the treatment and prevention of vitamin D deficiency.

What are the possible side effects of Cholecalciferol 20 000 IU Capsules?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Cholecalciferol 20 000 IU Capsules, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

Why are Cholecalciferol 20 000 IU Capsules approved?
The use of cholecalciferol in the prevention and treatment of vitamin D deficiency is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Cholecalciferol 20 000 IU Capsules outweigh the risks and the grant of a marketing authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Cholecalciferol 20 000 IU Capsules?
A risk management plan has been developed to ensure that Cholecalciferol 20 000 IU Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Cholecalciferol 20 000 IU Capsules
The marketing authorisation for Cholecalciferol 20 000 IU Capsules was granted in the UK on 17 December 2014.

This summary was last updated in February 2015.

The full PAR for Cholecalciferol 20 000 IU Capsules follows this summary.

TABLE OF CONTENTS

I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Cholecalciferol 20 000 IU Capsules could be approved. This is a prescription only medicine (POM).

Cholecalciferol 20 000 IU Capsules are indicated in adolescents and adults for the treatment and prevention of vitamin D deficiency.
This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Malta as Concerned Member State (CMS). This application was made under Article 10a of Directive 2001/83/EC, as amended, claiming well-established use of the active substance.

Cholecalciferol is produced within the skin under the influence of UV radiation including sunlight. In its biologically active form, cholecalciferol 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 glands is inhibited directly by the biologically active form of cholecalciferol. PTH secretion is inhibited additionally by increased calcium uptake in the small intestine under the influence of biologically active cholecalciferol.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given this is a bibliographic application for a product containing an active substance of well-established use.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk Management Plan (RMP).

The lack of an Environmental Risk Assessment (ERA) with this application for a well-established product is acceptable.

The RMS and CMS considered that the application could be approved at Day 210 of the procedure on 13 November 2014. After a subsequent national phase, the marketing authorisation was granted in the UK on 17 December 2014.

II Quality aspects

II.1 Introduction

The hard gelatin capsules are ivory, opaque and unprinted and contain a clear, slightly yellow oily liquid.

The capsule shell comprises gelatin, titanium dioxide (E171) and yellow iron oxide (E172). The capsule contents comprise medium-chain triglycerides (from vegetable sources), butylated hydroxytoluene (BHT) and colloidal silicon dioxide.

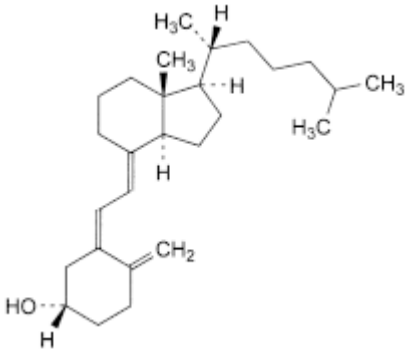
The capsules are stored in opaque, white PVC/PVdC blister packs with aluminium foil. Blister packs of 10, 14, 20, 28, 30, 56, 60, 84 and 100 capsules have been authorised, although not all pack sizes may be marketed.

II.2 Drug Substance

INN: Cholecalciferol

Chemical name: (5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3β-ol

Structure:



Molecular formula: $C_{27}H_{44}O$

Molecular weight: 384.64

With the exception of stability studies undertaken by the drug substance manufacturer, all aspects of the manufacture and control of the cholecalciferol are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical development

The aim of the pharmaceutical development of Cholecalciferol 20 000 IU Capsules was to develop an efficacious and stable formula, and with the minimum number of necessary excipients, using a lipid vehicle to dissolve the active in.

All excipients comply with their European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin, with the exception of the gelatin. A satisfactory declaration of compliance with current TSE/BSE regulations has been provided by the supplier of gelatin.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with commercial scale batches and is satisfactory.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data have been provided from commercial scale batches that comply with the release specification. Certificates of analysis have been provided for any working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 12 months.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

II.5 SmPC, PIL and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted marketing authorisations at a national level are available on the MHRA website.

The following product labelling was approved for use in the UK:

Blister:

Carton:


Aviticol™
20 000 IU
Capsules
Cholecalciferol
30 Liquid-filled capsules
Oral use
Quantum Pharmaceutical
BN:
EXP:
K0056
5 060380 960276
Each capsule contains 20 000 IU cholecalciferol, equivalent to 500 micrograms vitamin D_3.
Read the package leaflet before use.
Take as directed by your doctor.
Keep out of the sight and reach of children.
Store below 25°C.
Keep the blister in the outer carton in order to protect from light.
POM
Dispensing label
Marketing Authorisation Holder:
Colonis Pharma Ltd.
Hanover Place, 8 Church Road, Royal Tunbridge Wells, Kent, TN1 1JP, United Kingdom
Distributed by:
Quantum Pharmaceutical Ltd.
Quantum House, Hobson Industrial Estate, Burnopfield, County Durham, NE16 6EA, United Kingdom
PL 41344/0001

III Non-clinical aspects

III.1 Introduction

The applicant has provided suitable bibliographic information about the non-clinical aspects of the active substance, which is summarised as follows.

III.2 Pharmacology

Brief summary

Cholecalciferol plays an essential role in calcium and phosphate homeostasis, bone growth and cellular differentiation. It requires activation by sequential hydroxylations in the liver and kidney to 25-hydroxyvitamin D (25(OH)D) and then to the active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) before these actions can occur.

Pharmacology

Vitamin D exists in two forms; as ergocalciferol (Vitamin D_2) and cholecalciferol (Vitamin D_3). There are two sources of vitamin D for the body; it is either ingested from the diet (in the form of ergocalciferol and cholecalciferol) or cholecalciferol is synthesised in the skin via UVB irradiation, from sunlight, from its precursor 7-dehydrocholesterol.

Both forms of vitamin D are biologically inactive prohormones that must undergo successive hydroxylations at carbons 25 and 1 to form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), before they can bind to and activate the vitamin D receptor (VDR). Most effects of $1,25\text{-}(OH)_2D$ are mediated by VDR acting primarily by regulating the expression of genes whose promoters contain specific DNA sequences known as vitamin D response elements (VDREs). However, some actions of $1,25\text{-}(OH)_2D$ are more immediate, and may be mediated by a membrane bound vitamin D receptor that has been less well characterised than the nuclear VDR.

Cholecalciferol is essential in calcium and phosphate homeostasis, bone growth and cellular differentiation. The mechanism of action and the genes and receptors involved in the actions of vitamin D are discussed in the non-clinical overview. The effects of cholecalciferol on calcium-regulating and calcium non-regulating organs are discussed in adequate detail. Calcium regulating organs include intestine, kidney, bones and parathyroid glands; calcium non-regulating organs include skin, cardiac myocytes, pancreatic beta cells, lung and the immune system.

Conclusions on pharmacology

The pharmacology of cholecalciferol has been reported in published literature and was discussed adequately in the non-clinical overview.

III.3 Pharmacokinetics

Absorption

Cholecalciferol is well absorbed after oral administration, mainly from the small intestine. It is a fat soluble substance and is incorporated into the chylomicron fraction and absorbed through the lymphatic system.

Cholecalciferol is also formed in the skin from 7-dehydrocholesterol during exposure to sunlight, ultraviolet B (UVB) photons (290–315 nm). The absorption of UVB radiation causes 7-dehydrocholesterol to open its B ring, forming precholecalciferol. Precholecalciferol is unstable and rapidly undergoes rearrangement of its double bonds to form cholecalciferol. Cholecalciferol is ejected out of the plasma membrane into the extracellular space, where it enters into the dermal capillary bed, drawn in by the vitamin D binding protein (DBP).

Distribution
In the blood, vitamin D is transported bound to plasma proteins, mainly a specific alpha-globulin, DBP. Lipoproteins are more efficient than DBP to deliver the vitamin D synthesised in the skin to the hepatocyte for 25-hydroxylation, whereas lymph chylomicrons mediate the intestinal absorption and hepatic uptake of the vitamin D ingested in the diet.

Distribution of vitamin D appears to vary with tissue; there are tissues with high initial concentration and rapid decline (liver and serum), tissues where the accumulation and the decrease were slower (intestinal mucosa, kidney, bone and muscles) and tissues where the increase was slow, but no decrease was observed (adipose tissue).

Therefore, vitamin D is distributed into various tissues where it can be stored for prolonged periods and from which is it slowly released.

Vitamin D may also distribute into breast milk, although this is not mentioned in the non-clinical overview.

Metabolism
Vitamin D requires metabolic activation by hydroxylation (mainly) in the liver to 25-(OH)D, the major circulating form of vitamin D. 25-Hydroxylase activity has been found in both the liver mitochondria and endoplasmic reticulum, and the enzymatic activities appear to differ suggesting different proteins. 25-(OH)D is further hydroxylated in the kidney to 1,25-$(OH)_2$D, the biologically active form of vitamin D. The last step is catalysed by 25-(OH)D 1α-hydroxylase (CYP27B1), which is subject to tight regulation by PTH, calcium, phosphate and 1,25-$(OH)_2$D.
Further metabolism of 1,25-$(OH)_2$D occurs in the kidneys to other hydroxylated metabolites including 24,25-$(OH)_2D_3$ and also 23,25-$(OH)_2D_3$.

Excretion
Due to its high lipid solubility, cholecalciferol and its metabolites are only slowly eliminated from the body. Cholecalciferol has been reported to have a plasma half-life of 19 to 25 hours in man and a terminal half-life of weeks to months. 25-$(OH)D_3$ has an experimental elimination half-life of 19 days. The plasma ^{3}H-1,25-$(OH)_2D_3$ half-lives normally range from 20 to 30 hours. Metabolites are eliminated primarily (96%) through the bile and faeces, with a small proportion (<3%) of the dose eliminated via the urine as metabolites.

Conclusions on pharmacokinetics
The pharmacokinetics of cholecalciferol have been reported in published literature and were discussed adequately in the non-clinical overview.

III.4 Toxicology

Single dose toxicity and repeated-dose toxicity
Single dose toxicity and LD_{50} values have been published following oral administration of cholecalciferol to mice, rats, cats and dogs. In animals, clinical signs of acute toxicity can be seen at 0.5 mg/kg of cholecalciferol. Clinical signs (vomiting, lethargy, muscle weakness) seen within the first 48 hours of cholecalciferol overdose are due to the direct effect of increased plasma calcium concentrations on cells. These cellular effects include altered cell membrane permeability, altered calcium pump activity, decreased cellular energy production, and cellular necrosis. Specific organ effects include acute renal tubular necrosis, gastrointestinal stasis, increased gastric acid secretion, decreased skeletal muscle responsiveness, and decreased neural tissue responsiveness. The toxicity varies between species, but at endogenous levels, vitamin D is non-toxic.

In cats given commercial food supplemented with 15,000 IU (375 micrograms)/kg/day vitamin D_3, 8/10 treated cats died following 3-31 days of treatment. Clinical symptoms include anorexia, depression, weight loss, vomiting, polydipsia and dehydration. Soft tissue calcifications were observed in the treated but not control animals, with the coronary arteries apparently being the most susceptible. With longer duration of treatment, calcification of the bones and the aorta were observed in cats that had been fed commercial pet food containing 6,370 IU vitamin D/100 g (approximately 1600 micrograms/kg).

Hypervitaminosis D in humans as in animals is associated with hypercalcaemia and adverse effects are largely mediated by this condition. The severity of the symptoms and organ manifestations depend on the severity and length of the hypercalcaemia. Soft tissue calcification is a common effect, plus fatigue, excessive thirst, polyuria and poor mentation and even renal failure can appear.

Repeated dose studies in rats, dogs and monkeys have been reported in the literature, although only studies in humans and cats were discussed in the overview.

In rats given daily doses of 0, 5000, 10,000 or 20,000 IU vitamin D_3/kg body weight from 10 weeks of age, serum calcium and phosphorus levels and calcium excretion into urine were markedly increased. At the low and mid-doses, the rats showed occasional foci of kidney tubular calcification while this was more prevalent at the highest dose of 20,000 IU vitamin D_3/kg. At 26 weeks all kidneys from the highest dose showed mild to moderate nephrocalcinosis, while those in the other groups showed mild and nearly no calcinosis.

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

Genotoxicity
Cholecalciferol and 1,25-$(OH)_2D_3$ were both negative in an Ames test and 1,25-$(OH)_2D_3$ was also negative in an *in vivo* mouse micronucleus assay.

Carcinogenicity
Carcinogenicity studies have not been reported. Anti-proliferative activity has been reported for 1,25-$(OH)_2D_3$ in a number of studies.

Reproductive and developmental toxicity
The observation that female reproduction is markedly and significantly diminished in vitamin D deficiency was noted during the course of producing vitamin D deficient embryos. Thus, a reduction in fertility of 80% was found that could not be corrected by correcting the hypocalcaemia.

In the case of male reproduction, vitamin D deficiency also reduces the effectiveness of male fertility. This diminished male fertility can be corrected by additional calcium, raising plasma calcium concentration, which in turn restores fertility.

There was a statistically significant reduction in the number of litters delivered by mice given medium (1200 IU) and high (1800 IU) doses of cholecalciferol for 22 days during pregnancy compared with controls. Their litters also had reduced average length and weight.

Other studies on the effects on reproduction of high doses of cholecalciferol have been reported in the literature.

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.

High doses of cholecalciferol induced skeletal defects in rats, abnormal hearts in rabbits and microcephaly and skeletal anomalies in mice at oral or parenteral doses of 40,000 IU or higher.

Impurities
There is a relatively lengthy discussion of the residual solvents and excipients in the drug substance and product.

Five residual solvents are discussed, and are stated to meet the ICH limits for Class 2 and Class 3 solvents, tables of which have been included in the overview, taken from the ICH guideline Q3C (R5) on impurities; guideline for residual solvents (EMA/CHMP/ICH/82260/2006); not all of these are relevant.

The excipients used in manufacture of the product, medium-chain triglycerides, butylated hydroxytoluene, colloidal silicon dioxide, gelatin and purified water, are also discussed in detail in the overview; there are no concerns from the use of any of these excipients.

Conclusions on toxicology
The applicant's non-clinical overview has discussed the toxicity of cholecalciferol, although there is additional literature on repeated dose toxicity and reproductive toxicity that was not covered. Overall, the overview has presented an adequate picture of the toxicity of high levels of vitamin D and is acceptable. The residual solvents and excipients in the formulation are discussed and raise no toxicological concerns.

III.5 Ecotoxicity/environmental risk assessment (ERA)
In accordance with the CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2*), vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted from the need for environmental risk assessment because they are unlikely to result in significant risk to the environment. An environmental risk assessment is therefore not deemed necessary.

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

IV Clinical aspects

IV.1 Clinical pharmacology

IV.1.1 Pharmacokinetics

Absorption
Due to the nature of cholecalciferol absorption, the lipid content of food present in the gastrointestinal tract can influence absorption, as can intestinal fat malabsorption syndromes. A study where subjects received oral vitamin D doses of 1000 – 50 000 IU per day (both ergocalciferol and cholecalciferol) showed that taking the dose with the largest meal of the day improved absorption and results in approximately a 50% increase in serum levels of 25(OH)D across the range of doses. No difference was seen between the different dosage forms used in the study, oil based liquids and solid tablets.

A single dose pharmacokinetic study was performed. Within this study two 50 000 IU (totalling 100 000 IU) capsules were administered to 30 healthy subjects with a control group of 10 subjects to assess any seasonal change followed over a 4-month period. The clinical marker was serum 25(OH)D concentration. The dose used was 2.5 times the maximum single dose of the proposed product. The level of serum 25(OH)D concentration rose promptly after dosing, showing that such high doses are easily absorbed. Levels increased from a mean (± SD) baseline of 27.1± 7.7ng/mL to a concentration maximum of 42.0 ± 9.1ng/mL. The highest achieved concentration in any subject was 64.2ng/mL. There was no significant change from baseline in the control group (-0.72±0.80ng/mL).

In a comparative pharmacokinetic study of cholecalciferol and ergocalciferol tablets both products were administered as a single oral dose of 50 000 IU, a dose similar to that proposed in this application. Serum vitamin D concentrations were measured at days 0, 1 and 3. Baseline values of both vitamin Ds were low, with the cholecalciferol

concentration higher than the ergocalciferol, as would be expected. However, the rise by day 1 was essentially identical for both vitamin Ds, and at day 3 the serum levels of the two had fallen close to baseline and were virtually identical. These results indicate that absorption of the ergocalciferol and cholecalciferol at a dose of 50 000 IU was approximately equivalent.

In a study comparing serum levels of 25(OH)D after graded oral dosing in healthy men it was determined that there was linearity in the absorption of cholecalciferol. Cholecalciferol was administered at 0.025mg, 0.25mg or 1.25mg (1000 IU, 10 000 IU or 50 000 IU) per day for 8 weeks. The study also shows the direct correlation between increasing doses of cholecalciferol and the resulting increase in serum 25(OH)D.

Distribution
After absorption from ingestion of dietary intake, orally derived cholecalciferol is distributed differently to endogenously synthesised cholecalciferol, presenting to the liver with chylomicron carriers in the chyle; chylomicrons being small fat droplets composed of protein and lipid that serve to transport fat from the intestine to the liver and adipose tissue. A proportion of the orally derived cholecalciferol is then subsequently redistributed to other plasma carriers such as DBP. Due to their low solubility in the aqueous media of plasma, cholecalciferol is transported in the circulation bound to plasma proteins, the most important of which is the DBP. Cholecalciferol has a relatively low affinity for DBP estimated to be between 1×10^{-5} and 1×10^{-7} mol/L.

In a study it was observed that at approximately 8 nmol/L of serum cholecalciferol, about average for human adults, the concentration in adipose tissue is of the approximate magnitude as serum levels. This indicates that the adipose tissue reserves of the vitamin are effectively zero and that any additional cholecalciferol inputs are hydroxylated almost immediately. It also suggests that this is true for serum cholecalciferol concentrations up to 10-15 nmol/L, after which hepatic 25-hydroxylase starts to become saturated, resulting in an increase in stores of cholecalciferol in the adipose tissue.

The literature shows that cholecalciferol is well distributed around the human body, with excess reserves being held predominately within adipose tissue at the dose range within the proposed posology. It is also present in muscle. Cholecalciferol is available as the primary metabolite 25(OH)D in the serum.

Elimination

- **Excretion**

Because of their high lipid solubility, cholecalciferol and its metabolites are eliminated slowly from the body. A study investigated the excretion of vitamin D_3 and its metabolites. The plasma D3-3H (tritiated vitamin D_3) half-lives normally ranged from 20 to 30 hours. *In vivo* evidence that a metabolic transformation of vitamin D occurs was obtained, and a polar biologically active vitamin D metabolite was isolated from plasma.

Cholecalciferol has a plasma half-life of 19 to 25 hours and a terminal half-life of weeks to months. Calcifediol has an experimental elimination half-life of 19 days. Metabolites are eliminated primarily (96%) through the bile and faeces.

Excretion is adequately characterised.

- **Metabolism**

The liver and kidneys are the main sites for the metabolic activation of vitamin D_3. Vitamin D_3 is first hydroxylated at the 25-carbon atom by a vitamin D-25-hydroxylase enzyme. This reaction requires reduced nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen. In mammals the liver is the predominant site. The product of this hydroxylation, 25(OH)D, also known as calcidiol, is the principle circulating metabolite. Following the initial hydroxylation, 25(OH)D is carried from the liver, in plasma bound to an alpha 2 globulin and is transported to the kidney, where it undergoes a second hydroxylation before it becomes functional. The second hydroxylation is catalysed by $25(OH)D_3$-1-hydroxylase (1OH-ase) and produces $1,25(OH)_2D_3$ (calcitriol). This renal enzyme is found in the mitochondria of the proximal convoluted tubules and is rate limiting. Dihydroxy metabolite of vitamin D_3 is believed to stimulate intestinal calcium transport, intestinal phosphate transport, bone calcium mobilisation and other functions attributed to vitamin D. It prevents rickets, and is at least five times as biologically active as vitamin D_3 or $25(OH)D_3$. It functions at least three times faster than its precursors in promoting calcium absorption. The rate of conversion to $1,25(OH)_2D_3$ by the kidney is PTH-dependent. PTH is secreted in response to low plasma calcium levels.

The metabolism of vitamin D is adequately characterised.

Special populations

Impaired renal and hepatic function

Both forms of vitamin D are inactive and must undergo conversion in the liver and kidneys to form biologically active compounds. Ergocalciferol and cholecalciferol are hydroxylated by hepatic microsomal enzymes to 25(OH)D, also referred to as calcifediol. Further conversion of this intermediate form in the kidneys produces the physiologically active form, 1,25-dihydroxyvitamin D, or calcitriol. Vitamin D products are primarily eliminated through excretion in the bile. The mean elimination half-life of 1,25-dihydroxyvitamin D is 5 to 8 hours in adults.
It is, therefore, likely that in patients with impaired hepatic function a higher dosage of cholecalciferol would be required to maintain plasma vitamin D levels. These patients would therefore be at risk of a lack of efficacy from the treatment rather than a safety concern.

Elderly

An age-related decline in the absorption, transport or liver hydroxylation of orally consumed vitamin D_2 was observed. A comparison was made between a group of nine young men (aged 22 to 28 years) and a group of nine older men (aged 65 to 73 years), both groups had self-reported vitamin D intakes of less than 200 IU per day. The subjects were randomised to either a treatment group (received 1800 IU per day of ergocalciferol, Vitamin D_2) or to a control group. A significant interaction between the age of the subject and the supplement group was noted after three weeks.

Vitamin D in special populations is adequately characterised.

Interactions
Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D due to their ability to absorb lipophilic molecules. The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25(OH)D to 1,25(OH)D by the kidney enzyme, 25(OH)D-1-hydroxylase.

Potential PK interactions with vitamin D are adequately characterised.

Conclusions on pharmacokinetics
The pharmacokinetics of vitamin D are well established.

IV.1.2 Pharmacodynamics

Introduction
Vitamin D receptor (VDR) is a high-affinity receptor for $1,25(OH)_2D$. This 50- to 70-kDa protein facilitated association with nuclear chromatin, displayed saturable binding of $1,25(OH)_2D_3$, and had specificity for other vitamin D metabolites that precisely matched their *in vivo* biopotency. The VDR was found originally in the classic vitamin D target organs involved in mineral homeostasis: the intestine, bone, kidney, and the parathyroid glands. More recently, the VDR has been detected in many other tissues and cells types as well. These non-classic vitamin D target organs respond to $1,25(OH)_2D_3$ with a diverse range of biological actions including immunomodulation, the control of other hormonal systems, inhibition of cell growth, and induction of cell differentiation. The cellular response to 1,25(OH)D is mainly regulated by changing the cellular amount of VDR. Treatment with 1,25(OH)D increases the receptor level, presumably due to stabilisation of the receptor.

The most critical role of $1,25(OH)_2D_3$ in mineral homeostasis is to enhance the efficiency of the small intestine to absorb dietary calcium and phosphate as demonstrated conclusively in the VDR null mice. In the absence of VDR, normalisation of circulating levels of calcium and phosphorus through dietary supplementation corrected most of the phenotypic features of vitamin D resistance, including parathyroid gland growth, bone mineralisation, and growth plate histology. These findings concur with prior clinical observations in patients with vitamin D resistant rickets, whose bone abnormalities were resolved by calcium infusions.

Effects of vitamin D extend beyond calcium homeostasis. Receptors for calcitriol are distributed widely through the body. Vitamin D may improve muscle strength through a highly specific nuclear receptor in muscle tissue. In a study it was investigated whether there is an association between 25(OH)D concentrations and lower extremity function in ambulatory older persons, whether that association differs by activity level, and, if so, whether there is an identifiable threshold in the association.

Conclusions on pharmacodynamics
The pharmacokinetics of vitamin D are well recognised.

IV.2 CLINICAL EFFICACY

Introduction
The efficacy of low dose vitamin D regimes is well recognised.

Treatment
In the determination of dosing cholecalciferol when administered in daily doses up to 250 micrograms (10 000 IU) for a 20 week period it was found that in order to raise the serum 25(OH)D concentration by 1 nmol/l then 1 microgram (40 IU) of cholecalciferol should be administered orally.

Correction of vitamin D deficiency is associated with rapid improvement in bone density and may reduce fracture risk. Hence, treating vitamin D deficiency is important in the prevention and treatment of osteoporosis.

A recent meta-analysis identified 18 independent randomised controlled trials (15 of which were based in the EU) and included 57,311 participants. A total of 4777 deaths from any cause occurred during a trial size-adjusted mean of 5.7 years. Daily doses of vitamin D supplements varied from 300 to 2000 IU. The trial size-adjusted mean daily vitamin D dose was 528 IU. In nine trials, there was a 1.4- to 5.2-fold difference in serum 25-hydroxyvitamin D (25(OH)D) between the intervention and control groups. The summary relative risk for mortality from any cause was 0.93 (95% confidence interval, 0.87-0.99). There was neither indication for heterogeneity nor indication for publication biases. The summary relative risk did not change according to the addition of calcium supplements in the intervention.

Women aged 65 or older were given either cholecalciferol 300,000 IU once every three months or cholecalciferol 1000 IU daily for six months. All patients entering the study had documented vitamin D deficiency. After 3 and 6 months of treatment both groups had a significant increase in 25(OH)D and a reduction in PTH. Mean absolute increase at six months was higher in the group given 300,000 IU cholecalciferol intermittently. The percentage decrease of PTH was the same in both groups.

A study investigated that one year of either ergocalciferol or cholecalciferol dosing (1,600 IU daily or 50,000 IU monthly) did not produce toxicity, and 25(OH)D levels of less than 30 ng/ml persisted in approximately 20% of individuals despite good compliance. Substantial between individual response to administered ergocalciferol and cholecalciferol is observed.

In a study, a high-dose oral regimen for rapid correction of vitamin D deficiency was investigated, which made use of the calciferol 50 000 IU tablets available in that country. Thirty two women (67–84 years) with serum 25-hydroxyvitamin D concentrations less than 10 μg/l were treated with oral calciferol 50 000 IU daily for 10 days. It was concluded that this regimen provided a simple, safe and effective way of managing vitamin D deficiency.

In a study, cholecalciferol 300,000 IU was administered every 3 months, once at baseline and once at 3 months (intermittent D_3 group) or oral cholecalciferol 1 000 IU/day (daily D_3 group). All subjects received daily calcium supplements, depending on their dietary intake, to maintain a daily input of 1500mg. In a logistic regression

analysis, body mass index and type of treatment appeared to be significantly associated with normalisation of 25(OH)D values. Cholecalciferol 300 000 IU every 3 months was more effective than 1 000 IU daily in correcting vitamin D deficiency, although the two groups achieved similar effects on PTH at 6 months. Only 55% of the higher dose intermittent group reached desirable concentrations of 25(OH)D, suggesting that yet higher doses were required for adequate vitamin D repletion. Although the results show that both groups demonstrated a response to treatment, this was more in the subjects receiving intermittent cholecalciferol and the effect was observed in 55% of patients. In addition, all subjects are reported to have received supplemental calcium.

A study was conducted to compare the efficacy and safety of a 10-day, high-dose versus a 3-month, continuous low-dose oral cholecalciferol course in a vitamin D deficient population. The primary endpoints were the change in serum 25(OH)D concentrations at 3 months and the development of hypercalcaemia and hypercalciuria. Both the 10-day, high dose and the 3-month, low-dose cholecalciferol 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 study measured the effect of vitamin D supplementation, in vitamin D deficient women. In women who were less than 49 years and premenopausal there was no significant response to supplementation in either C-telopeptide or osteocalcin. It was concluded that correcting vitamin D deficiency in older women suppressed the age-induced increase in bone turnover and reduced the bone resorption which would normally be exacerbated in conditions of low serum 25(OH)D. This study was conducted in New Zealand in South Asian women. They were given a higher dose daily of cholecalciferol than proposed with this product. It can be seen that there is a benefit in supplementing patients known to be vitamin D deficient, to correct this hypovitaminosis, in this population. In addition, in older women, treatment suppresses bone turnover and resorption.

A placebo-controlled study was performed in patients undergoing haemodialysis where vitamin D is highly prevalent (94% of subjects ≤30ng/ml) (n=52). A high dose of 200 000 IU/week for three weeks was administered in these patients (n=25). At follow up 90.5% of subjects on active achieved serum 25(OH)D concentrations of >30ng/ml in contrast to the placebo group on 13.6%. There were no significant changes in serum calcium, phosphate or intact parathyroid hormone during the study. Such short-term high-dose oral cholecalciferol treatment in haemodialysis patients appeared to be effective with no evidence of toxic side effects.

Prevention

A randomised double-blind controlled trial comparing the effect of treatment of men and women aged 65 years and over living in the community with 100 000 IU oral vitamin D_3 or matching placebo every four months over 5 years on the rate of fractures in the UK was performed. 2686 subjects were randomised (2037 men and 649 women). The study was conducted by post and subjects sent their study medication by post every four months for the 5 year study period. Mean calcium intake at 4 years was 742mg/day and was not found to be different by treatment allocation. After 5 years, 268 men and women had incident fractures, of which 147

had fractures in common osteoporotic sites (hip, wrist or forearm, or vertebrae). Relative risks in the vitamin D group compared with the placebo group were 0.78 (95% confidence interval 0.61 to 0.99, P=0.04) for any first fracture and 0.67 (0.48 to 0.93, P=0.02) for first hip, wrist or forearm, or vertebral fracture. 471 participants died. The relative risk for total mortality in the vitamin D group compared with the placebo group was 0.88 (0.74 to 1.06, P=0.18). Findings were consistent in men and women and in doctors and the general practice population. This study looks at single treatment with vitamin D and shows there is a potential benefit in this population of patients. The dose used is however 100 000 IU every 4 months which is more convenient for subjects than the proposed 800 IU daily in this application. Other studies have suggested that receiving 800 IU daily may be more efficacious in increasing $25(OH)D_3$ levels than higher doses received infrequently. Although this supports single treatment with vitamin D, the applicant has not discussed how their proposed posology equates to a single treatment with 100,000 IU every 4 months.

A double-blind, placebo-controlled trial studied 2256 community-dwelling women of at least 70 years of age who were considered at high risk of fracture. They were randomly assigned to receive 500,000 IU of cholecalciferol or placebo each autumn to winter for 3 to 5 years. The main outcome measures were numbers of falls and fractures. Among older community-dwelling women, annual oral administration of high-dose cholecalciferol resulted in an increased risk of falls and fractures.

A prospective randomised double-blind trial to determine whether vitamin D supplementation decreases the incidence of hip fractures and other peripheral bone fractures was conducted in the Netherlands. Subjects were randomised to receive either active treatment with 400 IU vitamin D_3 or placebo. Study participants received study drug daily for 3 to 3.5 years. Compliance was checked by way of a questionnaire and by measurement of the serum 25(OH)D concentration. No important difference in baseline characteristics was found between the two groups. 2578 subjects were enrolled (1916 women, 662 men). These subjects were 70 years of age and over and living independently. Dietary calcium intake and 25 (OH)D were estimated in a subset of participants and found to be 868 mg/day. Mean serum 25(OH)D concentration in the third year was 23 nmol/L in the placebo group and 60 nmol/l in the vitamin D group. Hip fractures occurred in 48 people in the placebo group and 58 people in the vitamin D group (p = 0.39 ITT). Other peripheral fractures occurred in 74 people in the placebo group and 77 people in the vitamin D group (p=0.86).

Conclusions on clinical efficacy

It is generally recognised that the incremental rise in serum 25(OH)D in response to a given oral dose of cholecalciferol is inversely related to the baseline level of 25(OH)D. It is also generally recognised that the average increment of serum 25(OH)D has been estimated at 1.2 nmol/1 for every 1 microgram (40 IU) of cholecalciferol given as a daily oral dose when initiating levels are low, and an average increment of only 0.7 or less nmol/L when initiation levels are 70 nmol/L. A study demonstrated that when supraphysiological doses of vitamin D are used, vitamin D is stored in body fat and slowly released, to be converted to circulating 25(OH)D. However a recent study indicates that with large doses of 500,000 IU, the incidence of falls and fractures in the elderly may be increased. A study shows that different doses given in differing regimens are biochemically equivalent in terms of

efficacy. Other studies by other investigators demonstrate that clinical efficacy, measured through increases of the biochemical marker - serum 25(OH)D - is achieved through a range of doses from 5,000 IU to 150,000 IU, with an interchangeability of dosing regimen. The choice of regime can therefore be based on the physician's decision to optimise individual adherence.

These studies, well summarised by the applicant, along with the other comprehensive data supplied are considered adequate to demonstrate the efficacy of the requested posology. The discussion above about dosing and increasing serum levels further adds to this.

IV.3 CLINICAL SAFETY

Introduction
The safety of low dose vitamin D treatment is well established.

Vitamin D toxicity can result from regular excess in intake of this vitamin, and may lead to hypercalcaemia and excess bone loss. Individuals at particular risk include those with hyperparathyroidism, kidney disease, sarcoidosis, tuberculosis, or histoplasmosis. Chronic hypercalcaemia may lead to serious or even life-threatening complications, and should be managed by a physician. Early symptoms of hypercalcaemia may include nausea, vomiting, and anorexia (appetite/weight loss), followed by polyuria (excess urination), polydipsia (excess thirst), weakness, fatigue, somnolence, headache, dry mouth, metallic taste, vertigo, tinnitus (ear ringing), and ataxia (unsteadiness). Kidney function may become impaired, and metastatic calcifications (calcium deposition in organs throughout the body) may occur, particularly affecting the kidneys. Treatment involves stopping the intake of vitamin D or calcium, and lowering the calcium levels under strict medical supervision, with frequent monitoring of calcium levels. Acidification of urine and corticosteroids may be necessary.

In a meta-analysis the pooled estimate of the relative risk (RR) of discontinuing vitamin D treatment as a result of either symptomatic adverse effects or abnormal laboratory results was 1.37 (95% CI 1.01–1.88, p value 0.05, heterogeneity p value = 0.99). The RR of withdrawal was similar in the trials of standard vitamin D (RR 1.40, 95% CI, 0.94 to 2.06, p values = 0.10) and hydroxylated vitamin D (RR 1.34, 95% CI 0.80–2.24, p value = 0.27), respectively (p value on the difference between the two estimates of RR = 0.90). Excess vitamin D may lead to hypercalcaemia and hypercalciuria. Hypercalcaemia results in the deposition of calcium in soft tissues, diffuse demineralisation of bones and irreversible renal and cardiovascular toxicity. Moderate levels of vitamin D intake may enhance renal stone formation in predisposed individuals. It has been suggested that excess vitamin D may be linked to heart disease, but there is limited evidence for this. Data are available from a range of human supplementation studies, but the levels of vitamin D intake at which hypercalcaemia or hypercalciuria occurs vary between studies. Likely reasons for this include differences in populations studied; for example, several of the studies are in older people, a group vulnerable to vitamin D deficiency, while other studies are in younger adults, who are not likely to be vitamin D deficient. Individuals and groups are also likely to differ in their exposure to vitamin D sources other than supplementation, such as consumption of vitamin D-fortified foods and through

exposure to the sun. A safe upper level suitable for long-term intake by the whole population cannot be established based on the available data from studies in humans or animals. The human data are adequate to provide guidance. The highest level of vitamin D supplementation at which no effect on calcium was observed was 0.10 mg (4000 IU)/day. This was from a five month supplementation study of vitamin D_3 in 63 adults aged 23–56 years. In contrast, the lowest level of vitamin D_3 at which effects have been observed was 0.05 mg (2000 IU)/day from a 6 month study of supplementation with vitamin D (of unspecified form) in females above the age of 60 and males above the age of 65. Two out of the 63 subjects developed hypercalcaemia (serum calcium > 2.75 mmol/l). The reason for the difference is not known but may be due to difference in other sources of vitamin D exposure or in the study populations. Taking the evidence as whole, long-term exposures of up to 0.025 mg (1000 IU)/day vitamin D appear to be well-tolerated and may be necessary to prevent deficiency in some groups. Higher levels (for example, 0.045 mg (1800 IU)/day) may be tolerated without adverse effects over the short-term under medical supervision and may be necessary to correct a deficiency. The use of an uncertainty factor is not appropriate because the value is derived from an overview of a number of human studies which measured sensitive biochemical markers of calcium homeostasis. For guidance purposes only, a level of 0.025 mg (1000 IU)/day supplementary vitamin D would not be expected to cause adverse effects in the general population. This is equivalent to 0.0004 mg/kg body weight per day, for a 60 kg adult. Due to the difficulties in assessing total vitamin D exposure, an estimate for total intake has not been provided. Such an intake, or more, might well be required under medical supervision in managing overt or occult deficiency states. It should be noted that scaling on a body weight basis to children and infants may not be appropriate for vitamin D as it may lead to the recommended intake for an infant not being met.

Interactions
Concomitant use of glucocorticoids can decrease the effect of vitamin D. Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of cholecalciferol. Due to increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use.

Hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium and vitamin D. Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels. Rifampicin, barbiturates or phenytoin may reduce the activity of vitamin D_3, since they increase the rate of its metabolism.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D due to their ability to absorb lipophilic molecules.
The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25(OH)D to 1,25$(OH)_2$D by the kidney enzyme, 25(OH)D-1-hydroxylase.

Pregnancy
A recent study in 147 pregnant Iranian women has shown that 95.8% of the women were vitamin D deficient. The consequences of severe clinical vitamin D deficiency in

pregnancy can be life threatening to the newborn, while lesser degrees of hypovitaminosis D may have important long-term implications for offspring health.

In a pharmacokinetic study to assess the biochemical dose-response and tolerability of high-dose prenatal vitamin D_3 supplementation in Bangladesh, pregnant women at 27-30 weeks gestation (n=28) were randomised to 70 000 IU single dose, 35 000 IU/week or 14 000 IU/week until delivery. A control of non-pregnant women (n=16) were similarly administered vitamin D for a period of 10 weeks. In the study the serum 25(OH)D levels increased substantially to 80 nmol/l in 90% of pregnant cohort from a mean baseline of 35 nmol/l. During the study there were no supplement-related serious adverse events or hypercalcaemia.

Vitamin D deficiency correlates with pre-eclampsia, gestational diabetes mellitus, and bacterial vaginosis, and an increased risk for C-section delivery. Recent work emphasises the importance of non-classical roles of vitamin D in pregnancy and the placenta. The placenta produces and responds to vitamin D where vitamin D functions as a modulator of implantation, cytokine production and the immune response to infection. Past experiences with routine provision of 10 micrograms/day (400 IU/day) to all pregnant mothers suggest that this dose is sufficient to prevent overt neonatal complications of vitamin D deficiency. Recent data suggest that supplementation with dosages above 10 micrograms/day may be required for optimal health in the mother and child; however, further research is required for the assessment of the benefits and safety of supplementation with higher dosages. Lack of unified advice on vitamin D supplementation of pregnant mothers in the UK hinders the implementation of primary prevention strategies and is likely to leave some deficient mothers without supplementation.

Renal impairment
Serum 25(OH)D is metabolised in the kidney to $1,25(OH)_2D$, the active metabolite. There is a risk of vitamin D toxicity characterised by hypercalcaemia, hyperphosphataemia and oversuppression of PTH. Vitamin D administration is not contraindicated in patients with mild to moderate renal impairment, as long as adequate precautions and serum 25(OH)D monitoring is routinely undertaken. However, severe kidney insufficiency, simultaneous administration of any other vitamin D derivate, vitamin D overdosing or hyperactivity of the parathyroid gland make cholecalciferol treatment contraindicated.

Overdose
Overdose may cause hypercalcaemia as well as hypervitaminosis. Vitamin D toxicity is generally characterised by nonspecific symptoms such as nausea, vomiting, poor appetite, constipation, weakness, and weight loss. More seriously, it can also raise blood levels of calcium, causing mental status changes such as confusion and heart rhythm abnormalities.

Conclusions on clinical safety
The safety profile of vitamin D has been well described by the applicant, and includes data from clinical trials using doses similar to those requested for the proposed product. This information is reflected in the SmPC and is in line with the product information for other vitamin D products.

IV.4 Risk Management Plan

The applicant has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cholecalciferol 20 000 IU Capsules. Routine pharmacovigilance activities and risk minimisation measures should be adequate for this product, which contains a widely used active substance with a well-established safety profile.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypercalcaemia	Proposed text in SmPC: 4. 8. Depending on dose and duration of treatment of serious and persistent hypercalcaemia with acute (heart rhythm disturbances, nausea, vomiting, psychiatric symptoms, impaired consciousness) and chronic (increased urination, increased thirst, loss of appetite, weight loss kidney stones, kidney calcification, calcification outside in tissues the bone) episodes occur. Very rarely fatal courses have been described (see 4.4 "Special warning and precautions for use" and 4.9 "overdose").	Not proposed.
Hypercalciuria	Proposed text in SmPC: 4.3 Contraindication in existing hypercalcaemia and/or hypercalciuria, evidence of vitamin D toxicity or metastatic	Not proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	calcification. 4.4 Recommendation on calcium levels monitoring, close medical supervision when administering calcium supplements and caution in patients with higher risk of organ damage, age limit of 12 years and older 4.5 Interactions with impact on calcaemia and their management. 4.8 Hypercalcaemia and hypercalciuria listed 4.9 Symptoms of chronic overdose (usually leading to hypercalcaemia), overdose management	
Use in patients with conditions that modify vitamin D metabolism including sarcoidosis	Proposed text in SmPC: 4.4 Special warnings and precautions for use Use with care in patients with renal impairment, renal calculi or heart disease or arteriosclerosis who might be at increased risk of organ damage if hypercalcaemia were to occur.	Not proposed.
Interaction with thiazide diuretics	Proposed text in SmPC: 4.5. There is an increased risk of hypercalcaemia if vitamin D is administered with thiazide diuretics and calcium.	Not proposed.
Interaction with cardiac glycosides	Proposed text in SmPC: 4.5. Concurrent use of vitamin D analogues and cardiac glycosides may result in cardiac arrhythmias due to hypercalcaemia.	Not proposed.
Hypersensitivity	Proposed text in SmPC: 4.3 Cholecalciferol Capsules are contraindicated in: hypersensitivity to the active substance or to any of the excipients listed section 6.1	Not proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.4 Special warnings and precautions for use Cholecalciferol should be administered with caution to infants and patients who may have an increased sensitivity to its effects.	
Use in patients with hypervitaminosis D	Proposed text in SmPC: 4.3. Aviticol / Cholecalciferol Capsules are contraindicated in: Hypervitaminosis (toxicity against vitamin D)	Not proposed.
Use in patients with renal impairment (including nephrolithiasis or nephrocalcinosis)	Proposed text in SmPC: 4.4 Special warnings and precautions for use Use with care in patients with renal impairment, renal calculi or heart disease or arteriosclerosis who might be at increased risk of organ damage if hypercalcaemia were to occur.	Not proposed.
Use in pregnancy and lactation	Proposed text in SmPC: 4.6 Fertility, pregnancy and lactation <u>Pregnancy</u> There are no adequate data on the use of Aviticol/ Cholecalciferol in pregnant women. Aviticol/Cholecalciferol Capsules should not be used during pregnancy unless the clinical condition of the woman requires treatment with Aviticol/Cholecalciferol, at a dose necessary to overcome the deficiency. During pregnancy women should follow the advice of their medical practitioner as their requirements may vary depending on the severity of	Not proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	their disease and their response to treatment. Based on human experience and animal studies, vitamin D overdose causes physical and mental disability and congenital heart and eye conditions, due to hypercalcaemia, when administered during pregnancy. <u>Lactation</u> Cholecalciferol and its metabolites are excreted in breast milk. Overdose in infants induced by nursing mothers has not been observed. However, when prescribing additional vitamin D to a breast-fed child the practitioner should consider the dose of any additional vitamin D given to the mother.	
Potential for medication errors	The SPC and PIL for this strength provide an adequate description of the capsule and capsule contents. The product information also advises the user to store the blister foil in the original carton. These pieces of information will help minimise patients confusing this product with products of a lower concentration. The potential for misuse can never be completely excluded. Nonetheless, each patient must be carefully educated about the drug in terms of its potential	Not proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	risk of drug-drug and food-drug interactions. The package will comply with all the requirements given by current law and product information leaflet will be inserted. Additionally, the preparation is intended to be sold in pharmacies, i.e. the pharmacist should educate each patient adequately as well.	

Overdose	Other routine risk minimisation measures: 4.9 Overdose Acute or chronic overdose of Cholecalciferol can cause hypercalcaemia, an increase in the serum and urinary concentrations of calcium. The symptoms of hypercalcaemia are not very specific and consist of nausea, vomiting, diarrhoea often in the early stages and later constipation, anorexia, fatigue, headache, muscle and joint pain, muscle weakness, polydipsia, polyuria formation of renal calculi, nephrocalcinosis, kidney failure, calcification of soft tissues, changes in ECG measurements, arrhythmias and pancreatitis. In rare and isolated cases there are reports that hypercalcaemia is fatal. Treatment of overdose of hypercalcaemia due to vitamin D intoxication lasts several weeks. The recommendation for the treatment of hypercalcaemia is the avoidance of any further administration of vitamin D, including supplements, dietary intakes and the avoidance of sunlight. A low calcium or calcium-free diet can also be	Not proposed.

	considered. Rehydration and the treatment with diuretics e.g. furosemide to ensure adequate diuresis should be considered. Additional treatment with calcitonin or corticosteroids can also be considered.	

IV.5 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended.

V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet 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 product is acceptable and no new non-clinical or clinical safety concerns have been identified. Cholecalciferol is a well-established active substance. Extensive clinical experience with cholecalciferol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)