Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UK PAR

SoliCol D3 50,000 IU Tablets

(colecalciferol)

UK Licence No: PL 43196/0001

Pharmaceutics (UK) Limited

LAY SUMMARY

SoliCol D3 50,000 IU Tablets (colecalciferol)

This is a summary of the Public Assessment Report (PAR) for SoliCol D3 50,000 IU Tablets (PL 43196/0001). It explains how the application for SoliCol D3 50,000 IU Tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use SoliCol D3 50,000 IU Tablets.

For practical information about using SoliCol D3 50,000 IU Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are SoliCol D3 50,000 IU Tablets and what are they used for?

SoliCol D3 50,000 IU Tablets is a medicine with 'well-established use'. This means that the medicinal use of the active substance of SoliCol D3 50,000 IU Tablets is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

SoliCol D3 50,000 IU Tablets are is used for the treatment of Vitamin D deficiency.

How do SoliCol D3 50,000 IU Tablets work?

SoliCol D3 50, 000 IU Tablets are a vitamin product containing the active ingredient colecalciferol (Vitamin D_3). Vitamin D can be found in some foods and is also produced by the body when skin is exposed to sunlight. Vitamin D helps the kidneys and intestines absorb calcium and also build bones.

How are SoliCol D3 50,000 IU Tablets used?

Each SoliCol D3 50,000 IU Tablet contains 50,000 IU of colecalciferol (equivalent to 1.25 milligram of vitamin D_3). The tablets should be taken by mouth (orally). The tablets should not be chewed but swallowed whole with a glass of water, preferably together with a large meal.

This medicine should always be taken exactly as advised by the patient's doctor. If unsure, the patient should check with his/her doctor or pharmacist.

SoliCol D3 50,000 IU Tablets are not suitable for children and adolescents under the age of 18 years.

Please read section 3 of the package leaflet (PL) for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

SoliCol D3 50,000 IU Tablets can only be obtained on prescription from a doctor.

What benefits of SoliCol D3 50,000 IU Tablets have been shown in studies?

As colecalciferol is a well-known substance, and its use in the treatment of vitamin D deficiency is well-established, the applicant presented data from the scientific literature. The literature confirmed the efficacy and safety of colecalciferol in the treatment of vitamin D deficiency.

What are the possible side effects from SoliCol D3 50,000 IU Tablets?

Like all medicines, SoliCol D3 50,000 IU Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with SoliCol D3 50,000 IU Tablets, see section 4 of the package leaflet or the Summary of Product Characteristics available on the MHRA website.

Also, for the full list of restrictions, see the package leaflet.

Why are SoliCol D3 50,000 IU Tablets approved?

The use of SoliCol D3 50,000 IU Tablets in the 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 SoliCol D3 50,000 IU Tablets 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 SoliCol D3 50,000 IU Tablets?

A Risk Management Plan has been developed to ensure that SoliCol D3 50,000 IU Tablets 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 SoliCol D3 50,000 IU Tablets, 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/healthcare professionals will be monitored/reviewed continuously.

Other information about SoliCol D3 50,000 IU Tablets

A Marketing Authorisation for SoliCol D3 50,000 IU Tablets was granted in the UK to Pharmaceutics (UK) Limited on 18 December 2015.

The full PAR for SoliCol D3 50,000 IU Tablets follows this summary.

For more information about treatment with SoliCol D3 50,000 IU Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2016.

SoliCol D3 50,000 IU Tablets

(colecalciferol)

SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Pharmaceutics (UK) Limited a Marketing Authorisation for the medicinal product SoliCol D3 50,000 Tablets (PL 43196/0001) on 18 December 2015. The product is a Prescription Only Medicine (POM) and is indicated for the treatment of vitamin D deficiency.

The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use. The application is for a tablet formulation containing colecalciferol 50,000 IU (equivalent to 1.25 mg of vitamin D_3).

Colecalciferol is produced in the skin by conversion of 7-dehydrocholesterol to colecalciferol by ultraviolet light. In the absence of adequate sunlight exposure, colecalciferol is an essential dietary nutrient. Colecalciferol is converted to 25-hydroxy colecalciferol in the liver, and stored until needed. Conversion to the active calcium-mobilizing hormone 1,25-dihydroxy colecalciferol (calcitriol) in the kidney is tightly regulated. The principal action of 1,25-dihydroxy colecalciferol is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption.

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

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacturing and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of SoliCol D3 50,000 IU Tablets outweigh the risks and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

The application is submitted in accordance with Article 10a (well established use application) of Directive 2001/83/EC, as amended.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is available as off-white to yellowish oval tablets, debossed on one side with ‘3’. Each tablet contains 50,000 IU of colecalciferol BP (equivalent to 1.25 milligram of vitamin D_3). The product also contains DL-alpha tocopherol, modified food starch, medium-chain triglycerides, sodium ascorbate crystalline, silicon dioxide and sucrose.

The finished product is supplied in blisters composed of clear polyvinylchloride/Aclar polymer film and tempered aluminium foil. Each pack contains 10 tablets.

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

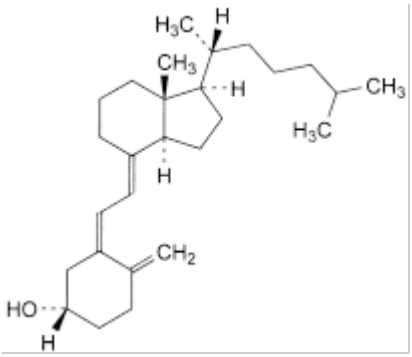
II.2 Drug Substance

Colecalciferol

INN: Colecalciferol

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

Structure:



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

Mr: 384.6

Appearance: White or almost white crystals.

Solubility: Practically insoluble in water, freely soluble in ethanol (96 percent), soluble in trimethylpentane and in fatty oils.

Colecalciferol is the subject of a European Pharmacopoeia monograph.

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

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable, tablets containing 50,000 IU of colecalciferol (equivalent to 1.25 milligram of vitamin D_3). Suitable pharmaceutical development data have been provided for this application.

With the exception of modified starch, all the excipients comply with the relevant European Pharmacopoeia monograph. Modified starch is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated at production scale and has shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months has been approved, with the special storage conditions ‘Store below 25°C. Keep the blister in the outer carton in order to protect from light.’ Suitable post approval stability commitments have been provided.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary for an application of this type.

II.4 Discussion on chemical, pharmaceutical and biological aspects

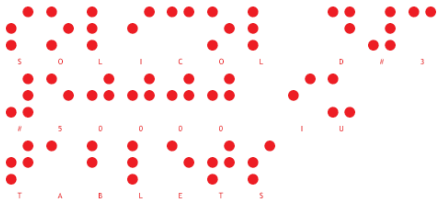
It is recommended that a Marketing Authorisation is granted for this application SoliCol D3 50,000 IU Tablets.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

solicol d#3
#50000 iu
tablets



Each tablet contains:
Colecalciferol 50,000 IU (equivalent to 1.25 milligrams of Vitamin D_3)

Contains Sucrose.
See leaflet for further information

For Oral Administration
Read the package leaflet before use.

Store below 25ºC.
Store blister in outer carton to protect from light.

Take as prescribed by the doctor

These tablets should not be chewed but swallowed with a glass of water.
Do not exceed the recommended dose.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN

Affix dispensary label here

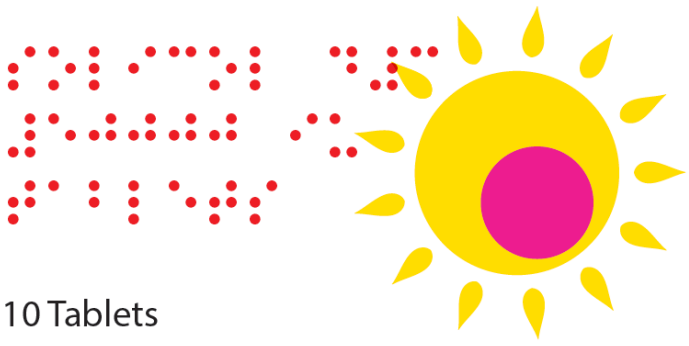
5 060414 860039 >

NON - VARNISHED
for BN & EXP

SoliCol D3® 50,000 IU Tablets
Colecalciferol

SoliCol D3® 50,000 IU Tablets
Colecalciferol

SoliCol D3® 50,000 IU Tablets
Colecalciferol



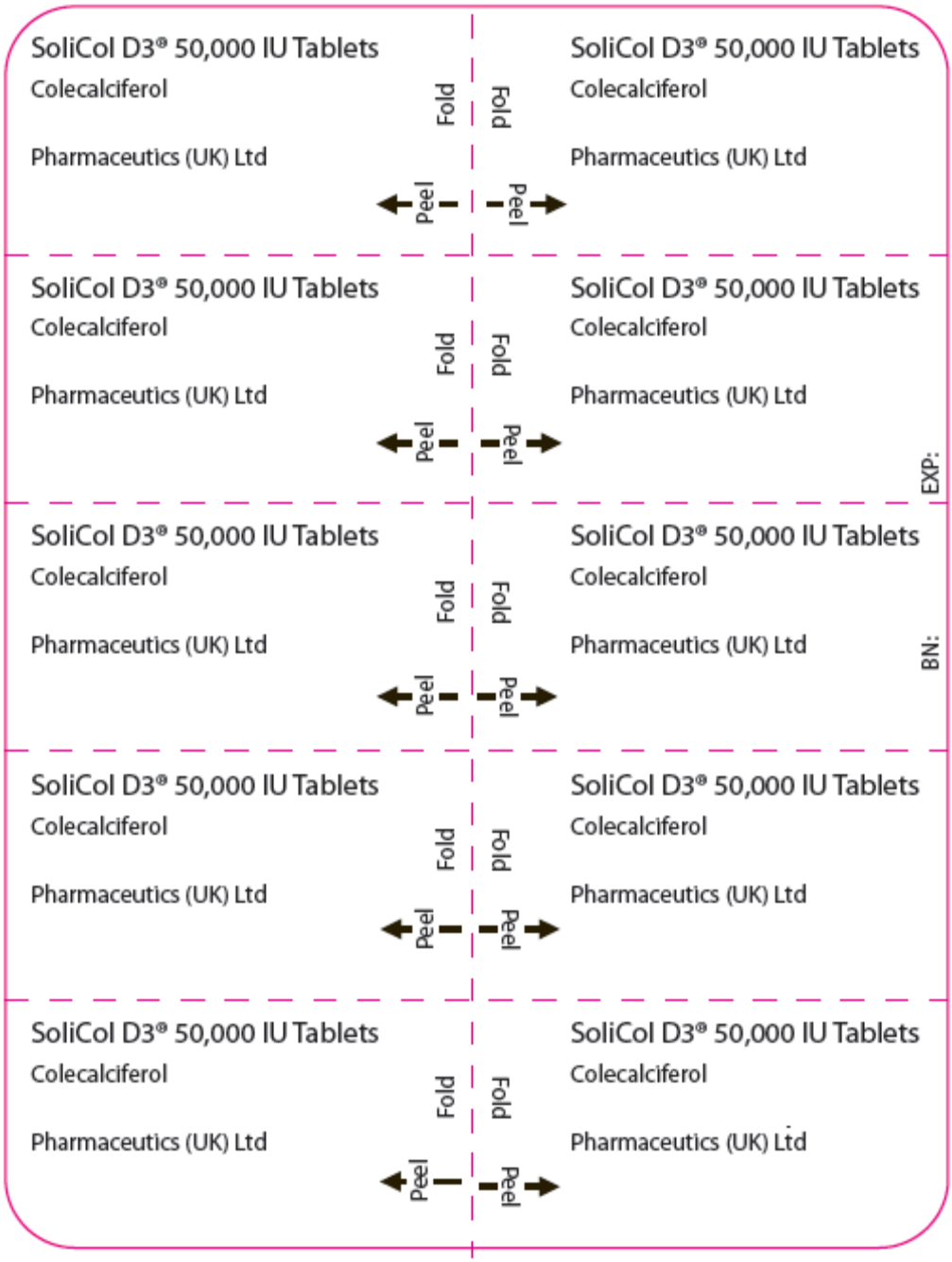
10 Tablets

Marketing Authorisation Holder:
Pharmaceutics (UK) Ltd
Unit A, 5 Boulton Road,
Reading, RG2 0NH
United Kingdom

POM

PL 43196/0001

Pharmaceutics (UK) Ltd


SoliCol D3® 50,000 IU Tablets
Colecalciferol
Pharmaceutics (UK) Ltd
Fold
Peel
EXP:
BN:

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of colecalciferol are well known and are adequately described in the applicant's non-clinical overview. No new non-clinical data were submitted and none are required for this bibliographic application.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacodynamics

The pharmacodynamic properties of colecalciferol are well known and are adequately described in the applicant's non-clinical overview.

III.3 Pharmacokinetics

The pharmacokinetic properties of colecalciferol are well known and are adequately described in the applicant's non-clinical overview.

III.4 Toxicology

The toxicological properties of colecalciferol are well known and are adequately described in the applicant's non-clinical overview.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This is acceptable as vitamins are unlikely to result in significant risk to the environment.

III.6 Discussion on the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for SoliCol D3 50,000 IU Tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a national application for a Marketing Authorisation for SoliCol D3 50,000 IU Tablets. The legal basis of this application is a well-established medicinal use application according to Article 10a of Directive 2001/83/EC as amended, supported by bibliographic literature.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

No new clinical pharmacokinetic data have been submitted and none are required for an application of this type. The pharmacokinetic profile of colecalciferol is well-known. Bibliographic pharmacokinetic data have been provided to support the application. An adequate summary of the pharmacokinetic profile of colecalciferol has been provided; this is provided below:

Absorption

Following cutaneous synthesis or oral consumption, vitamin D bioavailability is dependent on intestinal absorption, fat storage and metabolism. Absorption occurs primarily in the proximal small intestine and is influenced by gastric, pancreatic and biliary secretions, micelle formation, diffusion through the unstirred-water layer, brushborder-membrane uptake, and transport out of the intestinal cell. Any

process resulting in malabsorption of intestinal fat may therefore impair the absorption of vitamin D. Other conditions in which vitamin D absorption is impaired include liver failure, cystic fibrosis, Crohn's disease, and gastric bypass. Individuals taking bile acid-binding medications (such as cholestyramine and colestipol for hypercholesterolemia) will also have impaired vitamin D absorption.

Distribution
25OHD enters the circulation where it is transported by a globulin. It is the major circulating form of vitamin D and the molecule typically measured by clinicians wishing to assess vitamin D status since it reflects the cumulative effects of the vitamin intake and production by the sunlight. The rate and extent of the elevation of serum 25OHD levels following UV irradiation or vitamin D_3 ingestion are dependent on the regulated activity of vitamin D-25-hydroxylase and are thus variable. The serum half-life of 25OHD is approximately 15 days. 25OHD is not biologically active except at very high, nonphysiological levels.

Metabolism
25OHD is not biologically active except at very high, nonphysiological levels. Activation requires its conversion (second hydroxylation) to 1,25(OH)2D (calcitriol) in the kidney and other organs by the enzyme 25OHD-1α-hydroxylase. Calcitriol, is 500–1,000 fold more active than its precursor 25OHD. Production of 1,25(OH)2D is tightly regulated by a number of factors, the most important of which are serum phosphorus and parathyroid hormone (PTH) levels.

Circulating vitamin D_3 from either of the above two sources is subject to the same fate and is metabolized in the liver, by vitamin D-25-hydroxylase, one of several high-capacity cytochrome P-450 enzymes, to 25OHD (calcifediol). The microsomal enzymes CYP2R1, CYP2D11 and CYP2D25 are involved in the hydroxylation process in the liver but CYP2R1 appears to have the highest affinity for substrate vitamin D. The activity of vitamin D-25-hydroxylase is directly inhibited by 25OHD. This negative feedback mechanism helps maintain serum concentrations of 25OHD within a restricted physiological window – 75 to 220 nmol/L – in the face of significant variation in vitamin D ingestion and synthesis. Another effect of this negative feedback loop is that the rate of increase in serum 25OHD for a given oral dose of vitamin D is inversely related to the starting level of 25OHD.

Excretion
Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status

IV.3 Pharmacodynamics
The pharmacodynamics properties of colecalciferol are well-known. An adequate summary of the pharmacodynamic profile of colecalciferol has been presented in the clinical overview. A summary of the pharmacodynamics profile of colecalciferol is provided below:

Biologically active vitamin D, 1,25(OH)2D, is synthesised in two distinct systems. In addition to the classic two-step hydroxylation in the liver and kidneys, 1,25(OH)2D can also be produced locally by immune cells in response to infection. The bioactive vitamin D generated in these two pools apparently functions differently - while the former facilitates calcium adsorption and homeostasis, the latter confers immune regulation.

1,25(OH)2D produced by the kidneys enters the circulation and travels to its major target tissues the intestine and bone, where it interacts with its VDR to enhance intestinal calcium absorption and mobilise osteoclastic activity. The local production of 1,25(OH)2D in the non-calcium-regulating tissues, on the other hand, is thought to be for the purpose of regulating up to 200 genes, which helps to control cell growth and cellular differentiation and may be responsible for decreasing the risk of the cells being transformed into a malignant state. 1,25(OH)2D has been shown to inhibit cancer cell growth, induce

cancer cell maturation, induce apoptosis, and decrease angiogenesis. 1,25(OH)2D inhibits renin production in the kidney. The exact mechanism of vitamin D–mediated immune modulation remains unclear. The VDR is expressed in peripheral mononuclear cells and in both T-helper 1 (Th1) and T-helper 2 (Th2) cells. 1,25(OH)2D reduces the inflammatory response of Th1 cells and suppresses antigen presentation by dendritic cells, both of which are involved in the autoimmune response. 1,25(OH)2D increases expression of cathelicidin (LL-37), an antimicrobial peptide thought to be important for the innate immune system, especially against Mycobacterium tuberculosis.

Clinical Efficacy

No new efficacy data have been submitted and none are required for this type of application. The clinical efficacy of colecalciferol is well-established. Efficacy is adequately reviewed in the clinical overview; a summary relevant to the proposed indications are provided below:

Vitamin D deficiency:

The product's posology, dose (initial /maintenance) and monitoring are fully justified by published guidance and original publications and reviews. Data in support of the posology in adults and the children populations have been provided. The justification of use of vitamin D (high doses) in special groups is provided and supported with original and relevant data.

A study on the efficacy of different doses and time intervals of oral colecalciferol supplementation (600 IU/daily, 4,200 IU/weekly or 18,000 IU/monthly) with or without calcium in elderly nursing home residents demonstrated the poor vitamin D status often observed in institutionalised elderly, with 98% of the participants having a baseline serum 25OHD lower than 50 nmol/L. Oral vitamin D supplementation appeared to be effective in all the treatment groups; however, daily administration of vitamin D_3 supplementation was significantly more effective in increasing serum 25OHD levels and decreasing serum PTH levels than the weekly doses, whilst the monthly administration was the least effective. The percentage of participants with serum 25OHD <50 nmol/L after four months of supplementation was about 10% in the daily and weekly groups, but was more than 35% in the monthly group.

Significant rise in the 25OHD levels was observed after a single high dose of colecalciferol given either orally or intramuscularly in a randomised prospective study in Turkey that evaluated and compared the effects and safety of high dose (600,000 IU) intramuscular (IM) or oral colecalciferol on 25OHD levels, muscle strength and physical performance in 66 eligible vitamin D deficient/insufficient (25OHDlevels <30 ng/mL) ambulatory nursing home residents aged 65 years or older.

A randomised, double-blind trial on 63 elderly ambulatory participants (aged >65 years) demonstrated that large loading doses of vitamin D_3 rapidly and safely normalise 25OHD levels (>50 nmol/L) in the frail elderly. Three high-dose vitamin D_3 regimens were compared and evaluated: a 500,000-IU loading dose, the loading dose plus 50,000 IU/month, or 50,000 IU/month. The Loading and Loading+Monthly groups showed increases in 250HD of 58±28 nmol/L from baseline to 1 month. Thereafter, levels gradually declined to plateaus of 69±5 nmol/L and 91 ±4 nmol/L, respectively. In the Monthly group, 25OHD reached a plateau of ~80±20 nmol/L at 3-5 months.

In another study, vitamin D deficient (<25 nmol/L) elderly in-patients (n=33; mean age=80.5 ± 6.1 years) admitted for musculoskeletal pain, bone disease or gait abnormalities were treated with a single oral dose of 300,000 IU vitamin D_3 in combination with 500-1,000 mg calcium supplements per day depending on their dietary calcium intake. Baseline mean serum 25OHD concentrations were 15±5.5 nmol/L. The result showed that mean serum 25OHD serum concentrations increased to 81.4±29.7 nmol/L at 3 months (n=29) and were still 69.0± 17.9 nmol/L at 6 months (n=26). Mean serum calcium levels were 2.24± 0.11 mmol/L at baseline, 2.28±0.18 mmol/L at 3 months, and 2.28±0.13 mmol/L at 6 months. Despite a decline at 6 months, mean serum 25OHD concentrations were still more than 4 times, higher compared to baseline.

A prospective, randomised, open-label trial conducted in a clinical setting compared the efficacy and safety of a 10-day, high-dose (50,000 IU daily for 10 days) vs. a 3-month, continuous low dose (3,000 IU per day for 30 days followed by 1,000 IU per day for 60 days) of oral vitamin D3 in vitamin D deficient population (n=59; serum 25OHD at enrolment <50 nmol/L). Both groups also received calcium citrate 500 mg daily. The high-dose regimen was believed to be an effective and cheap alternative for patients with vitamin D deficiency. Twenty-six patients completed the study within 3±1 months. The mean increases in serum 25OHD were similar in both the high and low-dose groups (to 55 vs. 51 nmol/L, respectively; p=0.9). In both groups, 90% of patients achieved levels of 25OHD >50 nmol/L, and about 60% achieved levels of ≥75 nmol/L. There was no significant difference in the proportion of subjects who attained serum 25OHD concentrations >50 nmol/L between the high- and lowdose groups (9/10 vs. 13/14, respectively; p=1.0).

An investigation into the use of high bolus dose of vitamin D in vitamin D-insufficient patients (defined as <40 nmol/L) through two separate studies using oral vitamin D_3 in one and intramuscular vitamin D_2 in the other demonstrated that administration of a bolus dose of 300,000 IU vitamin D_3 (n=19) was practical, well-tolerated and safe, and offered greater potency than equimolar i.m. vitamin D_2 (n=50), with a higher and sustained serum 25OHD response and efficacious PTH suppression. The study with vitamin D_3 revealed that 100% and 89% of patients had serum 25OHD >50 nmol/L at 6 and 12 weeks, respectively, and the change in serum 25OHD from the baseline values was significantly greater (p <0.0001 and <0.0001 at 6 and 12 weeks, respectively). All patients with elevated baseline PTH were fully suppressed at 12 weeks, and no case of hypercalcaemia was observed.

IV.4 Clinical Safety

No new safety data were supplied or required for this bibliographic application. The safety profile of colecalciferol is well-known and has been adequately summarised by the Applicant in the clinical overview.

The data in support of the safety profile of vitamin D are derived from publications, reviews and publications of recognised bodies. Case reports which describe vitamin D toxicity are presented. A comprehensive review on drug interactions is described. The safety use in children and during pregnancy are discussed and a full review on overdose is cited. No new or unexpected safety issues arose from the submitted safety data.

Serum 25OHD concentrations causing adverse changes in calcium homeostasis, i.e. vitamin D intoxication, have been reported and exceed 500 nmol/L.

The upper limit or guidance concentrations for public safety are conservative at 25µg/day in the UK and 50 µg/day in the USA and Canada. A recent review of the literature has advocated the use of 25-50 µg/day of vitamin D to produce 25OHD concentration >75 nmol/L required for skeletal health and fracture prevention. Recent studies have demonstrated the safety of doses much higher, in the range of 100 µg (4,000 IU)/day and 250 µg (10,000 IU)/day. Some have proposed that adults require 50 µg (2,000 IU)/day to ensure adequate serum concentrations and to avoid deficiency.

The European Food Safety Authority (EFSA) has recently reviewed evidence and concluded that an upper limit of 4000 IU (100 µg) a day is safe for adults and children over 11 years of age.

High intakes of either vitamin D_2 or D_3 can cause toxicity through hypercalcaemia. The high serum calcium potentially leads to soft tissue calcification and resultant renal and cardiovascular damage. There is evidence that higher levels of vitamin D_2 can be tolerated compared to vitamin D_3. Patients with granulomatous disease are at risk of hypercalcaemia because of increased 1α-hydroxylase activity (which converts 25OHD to active 1,25[OH]2D). Toxicity has been reported during vitamin D treatment of tuberculosis and in patients with active sarcoidosis. Specialist advice should be sought before starting these patients on vitamin D therapy. In normal subjects, overall higher serum calcium concentrations

were seen with vitamin D treatment at 2400 IU per day and 3800 IU per day compared to the lower doses tested, but only in the higher dose group (3800 IU per day) did this exceed normal limits (10 mg/dL, 2.63 mmol/L).

There was an increased incidence of renal stones in the Women's Health Initiative study in those who were taking vitamin D with calcium supplements. Previous observational studies have shown that there is increased risk of renal stones with supplemental calcium intake, whereas dietary calcium intake may protect against this. There is no strong evidence that correcting vitamin D deficiency with vitamin D alone will increase the risk of renal stones. However patients with active nephrolithiasis should be managed on a case by case basis.

Excessive vitamin D intake is associated with significant clinical adverse effects, including pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting, and weight loss. These are all due to hypercalcaemia and occur only at very high vitamin D intakes. Hypercalciuria (defined as 24-hour calcium:creatinine molar ratios >1) may be a more sensitive indicator of vitamin D adverse effects than is hypercalcaemia. However, this ratio may change for reasons other than calcium or vitamin D effects; e.g., changes or differences in urinary creatinine unrelated to calcium metabolism will alter this ratio.

Drug interactions:
Vitamin D supplementation is contraindicated in situations of hypercalcaemia such as with sarcoidosis, metastatic bone disease, and conditions that have disordered vitamin D metabolism in activated macrophages such as Crohn's disease (active phase). Unusual syndromes in children, such as William's syndrome, may also predispose individuals to develop hypercalcaemia. Patients that regularly frequent tanning salons also need to be monitored as they have a propensity to develop high 25(OH)D values as a result of the ultraviolet waves used in the artificial tanning process, especially when consuming added vitamin D supplementation.

Catabolism of 25(OH)D and 1,25(OH)2D is primarily mediated by cytochrome P-450 enzymes. Concomitant use of medications metabolised by these enzymes are contraindicated during vitamin D supplementation. Of clinical relevance is the fact that long-term use of certain medications, including phenobarbital, phenytoin, carbamazepine, rifampicin, isoniazid and antiretrovirals (HAART), causes up-regulation of CYP3A4. This leads to decreased levels of 25(OH)D and 1,25(OH)2D, often resulting in clinically significant osteomalacia. Corticosteroids may counteract the effect of vitamin D.

Patients treated with thiazide diuretics are reported to be extremely sensitive to excessive vitamin D. There is an increased risk of hypercalcaemia if vitamin D is given with thiazide diuretics, calcium, or phosphate. In analysing the relation between thiazides and vitamin D, it is believed that thiazides are likely to be a risk factor for hypercalcaemia only in situations in which there is uncontrolled entry of calcium into the extracellular fluid, as, for example, in cases of multiple myeloma.

Pregnancy and Lactation:
Vitamin D and its metabolites are excreted in breast milk. The UK Health Departments recommend that all pregnant and breastfeeding women should take a daily supplement containing 10 µg (400 IU) of vitamin D, to ensure the mother's requirements for vitamin D are met and to build adequate foetal stores for early infancy.

There have been no published reports of the teratogenic effects of vitamin D on humans. Although some animal studies have shown dose-dependent maternal toxicity and teratogenesis (for example, growth impairment, skeletal malformations and cardiovascular anomalies), there are considerable limitations in extrapolating such findings to humans, in whom adverse fetal effects have not reportedly occurred following maternal ingestion of maintenance doses as high as 5 mg (200,000 IU) D_2 per day.

A randomised, double-blind, placebo-controlled trial in New Zealand has demonstrated that daily vitamin D supplementation with 1,000 or 2,000 IU vitamin D_3 during the last trimester of pregnancy can not only raise the serum 25OHD at week 36 significantly but also raises the proportion of babies born with 25OHD ≥20 ng/mL significantly, with the higher dose sustaining this increase for longer. Another recent randomised trial in Iran (n=51) concluded that a vitamin D_3 dose >50,000 IU/month is required during the second and third trimesters of pregnancy for vitamin D-deficient (<30 ng/mL) pregnant women in order for their neonates to achieve serum 25OHD levels > 20 ng/mL. Supplementation with <50,000 IU/month was found to be insufficient in ensuring a vitamin D level >20 ng/mL in all neonates born to vitamin D-deficient pregnant women. Yet another study on 160 vitamin D deficient (25OHD <30 ng/mL) pregnant women demonstrated that administration of 50,000 IU vitamin D_3 weekly for a total duration of 8 weeks starting at 26-28 weeks of pregnancy improves both maternal and neonatal calcium levels significantly compared to those administered only 400 IU vitamin D_3 daily. Safety of high loading dose of vitamin D_3 in pregnant women was demonstrated in a recent randomised placebo-controlled clinical trial in Bangladesh where 35,000 IU/week of vitamin D3 was administered to pregnant women (n=160). The weekly supplementation continued until delivery (median period of approximately 10 weeks.

Overdose:
There are numerous reports of accidental or uninformed consumption of very high doses of vitamin D. Of these reported cases of vitamin D toxicity, nearly all have involved doses higher than those used in the clinical trials; patients with compromised health, especially renal insufficiency; or confounding by hydrochlorothiazide treatment or other factors. These reports provide recent examples that confirm the acute toxic potential of elevated serum calcium concentrations caused by extraordinary intakes of vitamin D.

The classic symptoms of vitamin D toxicity include nausea, vomiting, constipation, thirst, polyuria, dehydration, apathy, lethargy and subsequent renal failure with death in rare cases. These are all due to hypercalcaemia and occur only at very high vitamin D intakes. Without laboratory evidence of hypercalcaemia and increased serum 1,25(OH)2D level, these signs of hypercalcaemia have been mistaken for gastroenteritis. The Women's Health Initiative (WHI) involving calcium and vitamin D_3 supplementation has raised concerns about the potential for this combination to increase the risk of renal stones. Chronic overdoses can lead to vascular and organ calcification as a result of hypercalcaemia. When excessive or toxic doses of vitamin D are administered, the most severe effects will be manifest during the period of administration. Treatment should consist of stopping all intake of vitamin D and rehydration

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to SoliCol D3 50, 000 IU Tablets.

Summary of safety concerns: None identified	
Important identified risks	• Hypercalcaemia • Hypercalciuria • Use in patients with conditions that modify vitamin D metabolism including sarcoidosis • Interaction with thiazide diuretics • Interaction with cardiac glycosides • Hypersensitivity • Use in patients with hypervitaminosis • Use in patients with renal impairment (including nephrolithiasis or nephrocalcinosis)
Important potential risks	• Use in pregnancy and lactation • Potential for medication errors • Overdose
Missing information	None

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for this application.

V. USER CONSULTATION

A 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 language used for the purpose of user testing the pack leaflet was English.

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

QUALITY

The important quality characteristics of SoliCol D3 50,000 IU Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type as the pharmacokinetics, pharmacodynamics and toxicology of colecalciferol are well-known.

EFFICACY
No new clinical data were submitted and none were required for this type of application.

The published literature supports the efficacy of the product in the proposed indication and posology. The efficacy of colecalciferol is well-known. The presented evidence for well-established use of the active substance is sufficient.

SAFETY
The safety profile of colecalciferol is well-known. The literature review identified no new or unexpected safety issues or concerns.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Colecalciferol is a well-known active substance. Extensive clinical experience with colecalciferol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.

STEPS TAKEN AFTER THE INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome