Public Assessment Report

UKPAR

Colecalciferol 20,000 IU Soft Capsules
(colecalciferol)

UK Licence No: PL 20491/0001

Tor Generics Limited
**LAY SUMMARY**

**Colecalciferol 20, 000 IU Soft Capsules**  
(colecalciferol)

This is a summary of the Public Assessment Report (PAR) for Colecalciferol 20,000 IU Soft Capsules (PL 20491/0001). It explains how Colecalciferol 20,000 IU Soft Capsules were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Colecalciferol 20,000 IU Soft Capsules.

This medicinal product will be referred to as Colecalciferol capsules in this lay summary for ease of reading.

For practical information about using Colecalciferol Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

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

Colecalciferol Capsules are used to treat or prevent vitamin D deficiency. Deficiency of vitamin D may occur when a diet or lifestyle does not provide a patient enough vitamin D or when the body requires more vitamin D (for instance during pregnancy). Colecalciferol Capsules may also be prescribed for certain bone conditions, such as thinning of the bone (osteoporosis) when it will be given to a patient with other medicines.

**How do Colecalciferol Capsules work?**
Colecalciferol Capsules contain the active ingredient colecalciferol (equivalent to 500 micrograms vitamin D₃). Vitamin D₃ acts to maintain normal concentrations of calcium and phosphate in plasma by facilitating their absorption from the small intestine, enhancing their mobilisation from bone and decreasing their excretion by the kidney.

**How are Colecalciferol Capsules used?**
Colecalciferol Capsules are taken by mouth. A single capsule should be swallowed whole with water, preferably with the main meal of the day.

The recommended dose in adults for prevention of vitamin D deficiency is 20,000 IU/month (1 capsule), higher doses may be required in certain situations.

The recommended dose in adults for the treatment of vitamin D deficiency is 40,000 IU/week (2 capsules) for 7 weeks, followed by maintenance therapy, (equivalent to 1,400-2,000 IU/day, such as 2-3 capsules per month), based on the advice of a doctor.

The recommended dose in children and adolescents (12-18 years) for prevention of vitamin D deficiency is 20,000 (1 capsule) every 6 weeks.

The recommended dose in children and adolescents (12-18 years) for the treatment of vitamin D deficiency is 20,000 IU (1 capsule) once every 2 weeks for 6 weeks.

Colecalciferol 20,000 IU Capsules should not be used in children under 12 years of age.
This medicine can only be obtained on prescription from a doctor.

For further information on how Colecalciferol Capsules are used, please refer to the Summary of Product Characteristics and the Patient Information Leaflet (PIL) available on the MHRA website.

**What benefits of Colecalciferol Capsules have been shown in studies?**
As colecalciferol 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 colecalciferol in the treatment and prevention of vitamin D deficiency.

**What are the possible side effects of Colecalciferol 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 Colecalciferol Capsules, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

**Why were Colecalciferol Capsules approved?**
The use of Colecalciferol Capsules in the treatment and prevention 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 Colecalciferol 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 Colecalciferol Capsules?**
A Risk Management Plan (RMP) has been developed to ensure that Colecalciferol 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 Colecalciferol Capsules 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 Colecalciferol Capsules**
A Marketing Authorisation was granted in the UK on 09 October 2017.

The full PAR for Colecalciferol Capsules follows this summary.

This summary was last updated in October 2017.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Tor Generics Ltd a Marketing Authorisation for the medicinal product Colecalciferol 20,000 IU Soft Capsules (PL 20491/0001) on 09 October 2017. This prescription only medicine (POM) is indicated, in adolescents, adults and the elderly, for treatment and prevention of vitamin D deficiency. It is also indicated as an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency.

This application was submitted under Article 10a, well-established use, of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Colecalciferol 20,000 IU Capsules contain the active substance colecalciferol. In its biologically active form vitamin D₃ 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 parathyroids is inhibited directly by the biologically active form of vitamin D₃. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active vitamin D₃.

No new non-clinical or clinical studies were necessary for this application, which is acceptable given that this is a bibliographic application for a product containing an active of well-established use. Bioequivalence studies are not necessary to support this application.

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.

A summary of the pharmacovigilance system and a detailed risk management plan have been provided with this application and these are satisfactory.
II QUALITY ASPECTS

II.1 Introduction

Each Colecalciferol 20,000 IU Soft Capsule contains 20,000 IU colecalciferol (equivalent to 500 micrograms vitamin D₃) as active ingredient. The excipients present in this product are refined sunflower oil and all-rac-α-tocopherol making up the capsule content. The capsule shell is composed of gelatin, glycerol and purified water.

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

The only excipient used that contains material of animal or human origin is gelatin. Satisfactory documentation has been provided by the gelatin suppliers stating that the gelatin they provide complies with the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’.

The finished product is packaged in polypropylene pots each fitted with a low density polyethylene (LDPE) cap, containing 20 capsules.

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

II.2 Drug Substance

INN: Colecalciferol

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

Structure:

Molecular formula: \( \text{C}_{27}\text{H}_{44}\text{O} \)

Molecular weight: 384.7 g/mol

Appearance: White or almost white crystalline powder.

Solubility: Practically insoluble in water, freely soluble in ethanol (96 per cent), acetone, chloroform; soluble in trimethylpentane and 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 aim of the development programme was to formulate safe, efficacious and stable capsules containing 20,000 IU colecalciferol.

Suitable pharmaceutical development data have been provided for this application.

**Manufacture of the product**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

**Finished Product Specification**

The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Stability of the product**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 18 months with storage conditions “Do not store above 25°C” and “Store this medicinal product in the original package in order to protect from light and moisture” have been set. These are satisfactory.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

The grant of a Marketing Authorisation is recommended.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**

Colecalciferol is a widely used, well-known active substance. Colecalciferol 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 D₃ (25(OH)D₃, or calcidiol) and then to the active form, 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃, or calcitriol) before these actions can occur.

**III.2 Pharmacodynamics**

**III.2.1 Primary pharmacodynamics**

Vitamin D exists in two forms; as colecalciferol (Vitamin D₃) and ergocalciferol (Vitamin D₂). Colecalciferol is produced by animal skin due to the action of ultraviolet radiation (290-310 nm) on 7-dehydrocholesterol. Ergocalciferol is found in plant sources; it differs from D₃ only in having a 22, 23 double bond and having an additional methyl group attached to carbon 24.

Both forms of vitamin D are biologically inactive prohormones that must undergo successive hydroxylations at carbons 25 and 1 before they can bind to and activate the vitamin D receptor. Colecalciferol is first hydroxylated to 25-hydroxyvitamin D₃ [25(OH)D₃, or calcidiol] in the liver and then to the active form, 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃, or calcitriol] in the kidney by the enzyme vitamin D 1α-hydroxylase. Calcitriol enhances the intestinal absorption of calcium. Ergocalciferol (vitamin D₂) undergoes the same two-stage activation process, involving first 25-hydroxylation in the liver to form 25(OH)D₂ followed by 1α-hydroxylation in the kidney to form the biologically active molecule 1,25(OH)₂D₂. Colecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂) together are described as vitamin D.
The main mechanism of action of vitamin D is the interaction of 1,25(OH)D with the nuclear vitamin D receptor (VDR), which heterodimerises with retinoid X receptor (RXR) and acts as a ligand-activated transcription factor by binding to genomic vitamin D responsive elements (VDRE) in vitamin D-regulated genes. These include more than 50 other genes important for mineral homeostasis, vitamin D metabolism, energy metabolism, cell differentiation and proliferation, extracellular matrix proteins, oncogenes, growth factors, signal transduction proteins and peptide hormones. Genes can be upregulated or downregulated. Amongst the genes that are downregulated are parathyroid hormone (PTH), osteocalcin, protein-kinase A inhibitors and interleukin-2 genes.

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

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

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

III.2 Secondary pharmacodynamics & Safety pharmacology
In addition to its role in calcium homeostasis, colecalciferol has widespread effects on cellular differentiation and proliferation, can modulate immune responsiveness, regulation of hormone secretion and central nervous system function.

III.2.3 Pharmacodynamic drug interactions
It has been shown in rat studies that vitamin A may antagonise the actions of vitamin D. Increasing the dietary level of retinyl acetate caused a progressive decrease in the total amount of ash in the femur and increase in epiphyseal plate. Elevation of plasma magnesium increases the secretion of PTH, which stimulates the synthesis of 1,25(OH)₂D. Magnesium deficiency in humans may result in an impaired PTH secretion followed by hypocalcaemia and a reduced serum concentration of 1,25(OH)₂D.

III.2.4 Overall conclusions on pharmacology
The pharmacology of vitamin D is well known and described in the literature, and the review provided in the dossier is comprehensive and is considered to be sufficiently comprehensive and detailed.

III.3 Pharmacokinetics
III.3.1 Absorption
Colecalciferol is well absorbed after oral administration, mainly from the small intestine. Colecalciferol is a relatively non-polar molecule and needs to be solubilised by incorporation into bile-salt micellar solutions for absorption to occur via the gastro-intestinal tract. Absorption of [³H]-vitamin D in normal subjects was shown to be 62-91% of the dose. Various conditions in humans can reduce its absorption e.g. coeliac disease, biliary obstruction absorption, chronic pancreatitis, liver failure, cystic fibrosis, Crohn’s disease and gastric bypass.

III.3.2 Distribution
The lipophilic nature of colecalciferol, taken up by adipocytes, explains its relatively long half-life in the body of ~2 months. The metabolite, 25-hydroxyvitamin D₃, has a half-life of ~15 days and the active metabolite, 1α,25(OH)₂D₃ has a half-life of ~15 hours.

To investigate the possibility of specific intrauterine transfer and storage of vitamin D in fetal tissues, vitamin D-deficient female rats were given depot injections of 3H- or 14C-labeled cholecalciferol before mating and the 3H-labeled animals were killed at stages during the last third of gestation. Analysis of lipid extracts from whole foetuses revealed a linear increase in the concentration of 25-hydroxyvitamin D₃, 24,25-dihydroxyvitamin D₃, and D₃ itself between days 14 and 19 of gestation.

### III.3.3 Metabolism

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

The vitamin D₃ activating cytochrome P450s are CYP2R1, CYP27A1 and CYP27B1 and the catabolic cytochrome P450 is CYP24A1. There are differences between humans and rats in the CYP24A1-dependent metabolism of 1α,25(OH)₂D₃. CYP24A1 is integrally involved in the degradation of 25-hydroxyvitamin D₃ and 1α,25(OH)₂D₃ through side-chain hydroxylation and cleavage known as C-24 oxidation.

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

### III.3.4 Excretion

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

### III.3.5 Pharmacokinetic drug interactions

In view of the well-established clinical use of colecalciferol the clinical safety and efficacy profile is well-documented. Pharmacokinetic drug interactions investigations are therefore not necessary.

Ketoconazole, which inhibits 24-hydroxylase activity, markedly enhances the potency of 1,25(OH)₂D. Enhanced potency of 1,25(OH)₂D is also seen in 24-hydroxylase null mice. Thiazide drugs, which increase the tubular reabsorption of calcium, would enhance hypercalcaemic effects of a high dose of vitamin D. Glucocorticoids, phenobarbital and phenytoin antagonise the effect of vitamin D on intestinal calcium absorption. Individuals taking bile acid-binding medications, including colestyramine and colestipol, would be expected to have impaired vitamin D absorption.

### IV CLINICAL ASPECTS

### IV.1 Introduction

The Applicant has performed no pharmacokinetic studies. There is, thus, no comparison with previously available products on the market regarding bioavailability of vitamin D from the formulation. The applicant has reviewed available literature data on the effect of different formulations on vitamin D absorption.

In a randomised comparison after 4 weeks of daily supplementation with 10 μg cholecalciferol given as a fish oil capsule compared with the same dose of cholecalciferol given as a multivitamin tablet, carried out in 55 healthy subjects, mean 4-week increase in s-25(OH)D was 35.8 (95% CI 30.9, 40.8) nmol/l in
the multivitamin group and 32.3 (95 % CI 27.3, 37.4) nmol/l in the fish oil group; the mean difference was 3.5 (95 % CI - 3.6, 10.6) nmol/l (p = 0.33). The results were unaltered by statistical adjustment for body mass index (BMI), ethnic background, age and sex. It was concluded that fish oil capsules and multivitamin tablets containing 10 μg cholecalciferol administered over a 4-week period produced a similar mean increase in s-25(OH)D concentration [Holvik K, 2007].

More recently, a systematic review evaluating the effects of vehicle substances on vitamin D bioavailability, no critical differences were highlighted among different nutritional and pharmaceutical preparation with regard of the absorption of vitamin D [Grossmann RE, 2010].

Therefore, human in vivo data indicate that the absorption of vitamin D is not influenced by the kind of formulation chosen.

There are some data indicating that absorption may be optimised if vitamin D is taken with the major meal of the day, and that any differences between formulations with and without lipids are minimised if they are taken with a large meal [Mulligan GB, 2010; Raimundo FV, 2011]. A recommendation to take this product with the major meal is therefore included in the summary of product characteristics (SmPC) of the proposed product. It cannot be excluded that malabsorption syndrome might affect absorption of vitamin D₃. However, given that the SmPC recommends monitoring of 25-hydroxyvitamin D levels, the dosage can be tailored in these patients and a decreased absorption can be overcome.

The justification for the absence of a bioavailability study is considered acceptable and consistent with other 20,000 IU colecalciferol capsules approved in the UK.

IV.2 Pharmacokinetics
The Clinical Overview is considered to provide an adequate bibliographic review and critique of the pharmacokinetics of colecalciferol (Vitamin D₃).

IV.3 Pharmacodynamics
The Clinical Overview is considered to provide an adequate bibliographic review and critique of the pharmacodynamics of colecalciferol (Vitamin D₃).

IV.4 Clinical efficacy
Satisfactory bibliographic review and evaluation of the efficacy of colecalciferol (Vitamin D₃) has been provided.

IV.5 Clinical safety
The Clinical Overview is considered to provide an adequate bibliographic review and analysis of the safety of colecalciferol (Vitamin D₃).

Overall Conclusion
This is a bibliographic application. An extensive and adequate referenced clinical overview has been provided with this application. The justification for the absence of a bioavailability study is accepted.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder 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 Colecalciferol 20,000 IU Soft Capsules.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

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<th>Summary of Routine Risk Minimisation Activities</th>
<th>Summary of Additional Risk Minimisation Activities</th>
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<tr>
<td><strong>Safety concern</strong></td>
<td><strong>Summary of Routine Risk Minimisation Activities</strong></td>
<td><strong>Summary of Additional Risk Minimisation Activities</strong></td>
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<tr>
<td>Hypercalcaemia</td>
<td>Routine pharmacovigilance activities.</td>
<td>N/A</td>
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<tr>
<td>Hypercalciuria</td>
<td>Routine pharmacovigilance activities. Contraindication included in SmPC Section 4.3 Adverse event included in SmPC Section 4.8</td>
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<td>Use in patients with conditions that modify vitamin D metabolism including sarcoidosis</td>
<td>Routine pharmacovigilance activities. Contraindication included in SmPC Section 4.3 Warning included in SmPC Section 4.5</td>
<td>N/A</td>
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<td>Interaction with thiazide diuretics</td>
<td>Routine pharmacovigilance activities. Interaction included in SmPC Section 4.5</td>
<td>N/A</td>
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<tr>
<td>Interaction with cardiac glycosides</td>
<td>Routine pharmacovigilance activities. Warning included in SmPC Section 4.4 Interaction included in SmPC Section 4.5</td>
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<tr>
<td>Hypersensitivity</td>
<td>Routine pharmacovigilance activities. Contraindication included in SmPC Section 4.3 Adverse event included in SmPC Section 4.8</td>
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<td>Use in patients with hypervitaminosis D</td>
<td>Routine pharmacovigilance activities. Contraindication included in SmPC Section 4.3 Warning included in SmPC Section 4.4 Symptoms included in SmPC section 4.9</td>
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<tr>
<td>Use in patients with renal impairment (including nephrolithiasis or nephrocalcinosis)</td>
<td>Routine pharmacovigilance activities. Contraindication included in SmPC Section 4.3 Warning included in SmPC Section 4.4</td>
<td>N/A</td>
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**Important potential risks:**

| Use in pregnancy and lactation | Routine pharmacovigilance activities. Information included in SmPC Section 4.6 | N/A |
| Potential for medication errors | Routine pharmacovigilance activities. Product labelling and design of packaging | N/A |
| Overdose | Routine pharmacovigilance activities. | N/A |
Routine risk minimisation is provided through the summary of product characterisation and the patient information leaflet. No additional risk minimisation measures are planned for this product.

**Discussion on the clinical aspects**
The grant of a Marketing Authorisation is recommended for this application.

**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 language used for the purpose of user testing the PIL 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**
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with colecalciferol is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
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 approved labelling for Colecalciferol 20,000 IU Soft Capsules is presented below:
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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitment)

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