1. NAME OF THE MEDICINAL PRODUCT

Colecalciferol 20 000 IU Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains:

20 000 IU colecalciferol (equivalent to 500 µg vitamin D_3)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

3 PHARMACEUTICAL FORM

Capsule, Hard

Ivory opaque, unprinted, hard gelatin capsule containing a clear, slightly yellow oily liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Initial treatment of clinically relevant vitamin D deficiency in adults.

4.2 Posology and method of administration

One capsule contains 20 000 IU Colecalciferol (vitamin D_3).

Adult Posology

- Initial treatment of clinically relevant vitamin D deficiency:
  - 1 capsule twice per week (equivalent to 40,000 IU/week) for 7 weeks (corresponding to a loading dose of 280,000 IU).
- Maintenance therapy with lower doses of vitamin D equivalent to 800 to 1000 IU daily may be considered one month after the end of initial treatment with Aviticol 20,000 IU. For this purpose other preparations are available. The doctor in charge shall decide on the individual dosage and the duration of treatment.

Paediatric population

Aviticol 20,000 IU should not be used in infants or young children (under 12 years) as they may not be able to swallow the capsules and might choke. Instead, it is advisable to

use drops or dissolvable tablets. Due to the lack of data on posology the administration in adolescents between the ages of 12 – 18 years is not recommended.

Patients with renal impairment/hypercalcaemia
In the event of hypercalcaemia or signs of reduced renal function, the dose must be reduced or the treatment discontinued. If hypercalciuria occurs (more than 7.5 mmol equivalent to 300 mg calcium/24 hours), the dose is to be reduced or treatment discontinued.

Method of administration
This medicine is taken orally.
The capsule should be swallowed whole with water, preferably with the main meal of the day.

4.3 Contraindications

Colecalciferol 20 000 IU Capsules must not be used in patients with:

- Hypersensitivity to the active substance (colecalciferol) or to any of the excipients listed in section 6.1
- Hypercalcaemia and/or hypercalciuria
- Pseudohypoparathyroidism (The vitamin D requirement may be reduced by intermittent normal vitamin D sensitivity, with the risk of prolonged overdose)
- Nephrolithiasis (Renal calculi)
- Hypervitaminosis D
- Severe renal impairment
- Additional intake of preparations containing vitamin D

4.4 Special warnings and precautions for use

Colecalciferol 20 000 IU Capsules should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and other forms of vitamin D should be used.

Colecalciferol 20 000 IU Capsules should not be taken by patients with a tendency to form calcium-containing renal calculi.

Caution is required in patients receiving treatment for cardiovascular disease
(see section 4.5 – cardiac glycosides including digitalis).

Colecalciferol 20 000 IU Capsules should be prescribed with caution to patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active form. These patients should be monitored with regard to the calcium content in serum and urine.

During pregnancy, Colecalciferol 20,000 IU should be taken only when strictly indicated and dosed only as it is absolutely necessary to correct vitamin D deficiency (see section 4.6).

Allowances should be made for vitamin D supplements, other vitamin D containing medicines or from other sources.

The need for additional calcium supplementation should be considered for individual patients. Calcium supplements should be given under close medical supervision.

Medical supervision is required whilst on treatment to prevent hypercalcaemia.

During treatment with an equivalent daily dose exceeding 1,000 IU vitamin D the serum and renal calcium levels must be monitored and renal function checked via serum creatinine determination. Such monitoring is particularly important in elderly patients and during concomitant treatment with cardiac glycosides or diuretics (see section 4.5). This also applies to patients who are particularly susceptible to the formation of kidney stones that contain calcium.

Paediatric population

Colecalciferol 20,000 IU should not be used in infants or young children (under 12 years) as they may not be able to swallow the capsules and might choke. Instead, it is advisable to use drops or dissolvable tablets. Due to the lack of data on posology the administration in adolescents between the ages of 12-18 years is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Phosphate infusions should not be administered to lower hypercalcaemia of hypervitaminosis D because of the dangers of metastatic calcification.

Patients treated with cardiac glycosides may be susceptible to high calcium levels and should have ECG parameters and calcium levels monitored. It is recommended to reduce the dose or interrupt treatment if the calcium content in the urine exceeds 7.5 mmol/24 hours (300 mg/24 hours).

Simultaneous administration of benzothiadiazine derivatives (thiazide diuretics) increases the risk of hypercalcaemia because they decrease the calcium excretion in the urine. The calcium levels in plasma and urine should therefore be monitored for patients undergoing long-term treatment.

If colecalciferol is combined with metabolites or analogues of vitamin D careful monitoring of serum calcium levels is recommended.

Anti-convulsants e.g. phenytoin, phenobarbital, primidone may diminish the effect of colecalciferol due to hepatic enzyme induction.

Rifampicin may reduce the effectiveness of colecalciferol due to hepatic enzyme induction.

Isoniazid may reduce the effectiveness of colecalciferol due to inhibition of the metabolic activation of colecalciferol.

Drugs leading to fat malabsorption, e.g. orlistat, liquid paraffin, cholestyramine, may impair the absorption of colecalciferol.

The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.

Concomitant use of glucocorticoids can decrease the effect of vitamin D.

4.6 Fertility, pregnancy and lactation

Pregnancy

During pregnancy, Colecalciferol 20,000 IU should be taken only when strictly indicated and dosed only as it is absolutely necessary to correct vitamin D deficiency. Overdoses of vitamin D must be avoided during pregnancy, as prolonged hypercalcaemia may lead to retardation of physical and mental development, supravalvular aortic stenosis and retinopathy in the child.

Breast-feeding

Colecalciferol 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.

Fertility

Normal endogenous levels of vitamin D are not expected to have any adverse effects on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. Colecalciferol has no known side effects that are likely to affect the ability to drive and use or operate machines.

4.8 Undesirable effects

Adverse reactions are listed below, by system organ class and frequency.

MedDRA System Organ Class	Frequency Category	
	Uncommon (affecting les than 1 in 100 people)	Rare (affecting less than 1 in 1000 people)
Metabolism and nutrition disorders	Hypercalcaemia Hypercalciuria	
Skin and Subcutaneous disorders		Pruritus Rash Urticaria

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via The Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

4.9 Overdose

Acute or chronic overdose of colecalciferol 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

A normalisation 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 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.

Phosphate infusions should not be administered to lower hypercalcaemia of hypervitaminosis D because of the dangers of metastatic calcification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues ATC code: A11CC05

Absorption: Colecalciferol is easily absorbed in the small intestine.

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

Elimination: Colecalciferol and other forms of vitamin D are excreted in faeces and urine.

5.2 Pharmacokinetic properties

The pharmacokinetics of colecalciferol have been widely studied and are well-known. Colecalciferol from nutritional sources is almost completely absorbed from within the gastro-intestinal tract in the presence of dietary lipids and bile acids. Colecalciferol is stored in fat cells and its biological half-life is approximately 50 days.

Colecalciferol is metabolised by microsomal hydroxylase to form 25-hydroxycolecalciferol ($25(OH)D_3$, calcidiol), the primary storage form of vitamin D_3. $25(OH)D_3$ undergoes a secondary hydroxylation within the kidney to form the predominant active metabolite 1,25-hydroxycolecalciferol ($1,25(OH)_2D_3$, calcitriol). The metabolites circulate in the blood bound to a specific α-globin.

After a single oral dose of colecalciferol, the maximum serum concentrations of the primary storage form are reached after approximately 7 days. $25(OH)D_3$ is then slowly eliminated with an apparent half-life in serum of about 50 days. Colecalciferol and its metabolites are excreted mainly in the bile and faeces.

After high doses of colecalciferol, serum concentrations of $25(OH)D_3$ may be increased for months. Overdose-induced hypercalcaemia may persist for weeks (see 4.9 "Overdose").

5.3 Preclinical safety data

Colecalciferol overdosage in animals has been shown to induce malformations in rats, mice and rabbits at doses significantly higher than the human dose. The malformations included skeletal defects, microcephaly and cardiac malformations.

At doses equivalent to those used therapeutically, colecalciferol has no teratogenic activity.

Colecalciferol has no potential mutagenic or carcinogenic activity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Medium-chain Triglycerides (from vegetable sources)

Butylated Hydroxytoluene (BHT)

Colloidal silicon dioxide

Capsule shell:

Gelatin

Titanium dioxide (E171)

Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Opaque, white PVC/PVdC blister packs with aluminium foil.

Pack sizes: 10, 14, 20, 28, 30, 56, 60, 84 and 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal. Any unused product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Colonis Pharma Limited
Quantum House
Hobson Industrial Estate
Burnopfield
County Durham
NE16 6EA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 41344/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/12/2014

10 DATE OF REVISION OF THE TEXT

26/04/2018