1. PRODUCT NAME

Vit.D3, 1.25mg (equivalent to 50,000IU), soft gelatin capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vit.D3 soft gelatin capsule contains Colecalciferol Ph Eur Vitamin D3 1.25mg (equivalent to 50,000IU). For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Vit.D3 capsules are presented as natural coloured, transparent, oval shaped, soft gelatin capsules, containing pale yellow coloured oil.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Colecalciferol is indicated for treatment of vitamin D deficiency associated with malabsorption in children and/or adult patients.

Colecalciferol is indicated for prevention and treatment of vitamin D deficiency states. Vitamin D deficiency may occur as a result of inadequate nutrition, intestinal malabsorption, or lack of exposure to sunlight, but does not occur in healthy individuals receiving an adequate balanced diet and exposure to sunlight.

Requirements may be increased and / or supplementation may be necessary in the following persons or conditions (although clinical deficiencies are usually rare):

Alcoholism.

Dark-skinned individuals.

Hepatic-bilary tract disease – hepatic function impairment, cirrhosis, obstructive jaundice.

Infants, breast-fed, with inadequate exposure to sunlight.

Intestinal disease – celiac, tropical sprue, regional enteritis, persistent diarrhoea.

Lack of exposure to sunlight combined with reduced vitamin D intake.

Renal function impairment.

In general, vitamin D absorption will be impaired in any condition in which fat malabsorption (steatorrhoea) occurs.

Some unusual diets, (e.g., strict vegetarian diets with no milk intake such as vegan-vegetarian or macrobiotic, or reducing diets that drastically restrict food selection) may not supply minimum daily requirements of vitamin D. Supplementation may be necessary in patients receiving total parenteral nutrition (TPN) or undergoing rapid weight loss or in those with malnutrition, because of inadequate dietary intake.

Congenital rickets have been reported in newborns whose mothers had low serum levels of vitamin D.

4.2 Dose and method of administration

1) Moderate/Severe Vitamin D insufficiency is less than 10 micrograms/litre of serum 25 hydroxy Vitamin D concentration

   Dosage = 1 x Colecalciferol tablet a day for 10 days (loading), then

   1 x Colecalciferol tablet a month (maintenance)

2) For Mild/Moderate Vitamin D insufficiency, i.e. 10mcg/L or higher

   Dosage = 1 x Colecalciferol tablet a month

Before vitamin D therapy is begun, elevated serum phosphate concentrations must be controlled.

Clinical response to vitamin D depends on adequate dietary calcium.

Because of individual variation in sensitivity to its effects, dosage of vitamin D must be adjusted on the basis of clinical response. Some infants are hyper reactive to even small doses. Careful titration is necessary to avoid overdosage, which induces hypercalcaemia and can cause hypercalciuria and hyperphosphataemia.

Dosage of vitamin D from dietary and other sources should be evaluated in determining the therapeutic dosage.

The serum calcium times phosphorus (Ca X P, in mg/dL) product should not exceed 60.

To control elevated serum phosphate concentrations in patients undergoing dialysis, a phosphate binding agent should be used. The dosage of the binding agent may need to be increased during vitamin D therapy since phosphate absorption is enhanced.

Deficiency due to malabsorption states or liver disease often requires higher doses for treatment, of up to 1 mg (40 000 units) daily. Doses of up to 2.5mg (100 000 units) daily may be used in the treatment of hypocalcaemia due to hypoparathyroidism.

Colecalciferol does not need to be administered with food.

PATIENT MONITORING:

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition:

Blood urea nitrogen (BUN) and

Creatinine, serum

Determination recommended at periodic intervals in patients receiving therapeutic doses.

Alkaline phosphatase concentrations, serum, and

Phosphorus concentrations, serum, and

Calcium concentrations, urinary, 24-hour, and

Calcium / creatinine, urinary ratio

Determination recommended every 1 to 3 months during therapy, as long as the patient remains stable.

Calcium concentrations, serum, or ionised calcium concentration, serum

Determinations recommended at least once weekly in early period of treatment to aid in dosage adjustment because of narrow therapeutic range, then at periodic intervals during therapy in patients receiving therapeutic doses; serum calcium concentrations should be maintained at 8.8 to 10.3mg per 100mL, depending on lab variability; serum ionised calcium concentrations are preferable to determine free and bound calcium, but may not be readily available.

X-rays of bones

Recommended by some clinicians every 3 to 6 months until patient is stable, then yearly to determine when treatment of familial hypophosphataemia or hypoparathyroidism is sufficient.

4.3 Contraindications

Colecalciferol is contraindicated in patients with hypersensitivity to any component of this product. Vit.D3 capsules contain soya oil. If you are allergic to peanut or soya, do not use this product.

Except under special circumstances, this medication should not be used when the following medical problems exist:

- Hypercalcaemia
- Hypervitaminosis D
- Renal osteodystrophy with hyperphosphataemia (risk of metastatic calcification; however, vitamin D therapy can begin once serum phosphate levels have stabilised).

Risk-benefit should be considered when the following medical problems exist:

- Arteriosclerosis or Cardiac function impairment (conditions may be exacerbated due to possibility of hypercalcaemia and elevated serum cholesterol concentrations).
- Hypersensitivity to effects of vitamin D (may be involved in causing idiopathic hypercalcaemia in infants).
- Renal function impairment (toxicity may occur in patients receiving vitamin D for non-renal problems, although toxicity is also possible during treatment of renal osteodystrophy because of increased requirements and decreased renal function).
- Sarcoidosis, and possibly other granulomatous diseases (increased sensitivity to effects of vitamin D).

4.4 Special warnings and precautions for use

Studies have shown that the elderly may have an increased need for vitamin D due to a possible decrease in the capacity of the skin to produce pre-vitamin D3, or a decrease in exposure to the sun or impaired renal function or impaired vitamin D absorption.

4.5 Interaction with other medicines and other forms of interaction

There is an increased risk by hypercalcaemia if vitamin D is co-administered with thiazide diuretics and calcium. Plasma-calcium concentrations should be monitored in patients receiving the drugs concurrently. Some antiepileptics may increase vitamin D requirements (e.g. carbamazepine, phenobarbitone, phenytoin, and primidone).

Requirements may be increased by the following medications: Barbiturates, cholestyramine, colestipol, hydantoin anticonvulsants, mineral oil, and primidone.

A case of severely decreased prothrombin has been reported as due to a possible interaction of vitamin D with warfarin and calcium carbonate.

4.6 Fertility, pregnancy and lactation

Fertility:

Fertility clinical data is not available.

Pregnancy:

Problems in humans have not been documented with intake of normal daily requirements. Maternal hypercalcaemia during pregnancy in humans may be associated with increased sensitivity to effects of vitamin D, suppression of parathyroid function, or a syndrome of peculiar (elfin) faces, mental retardation and congenital aortic stenosis in infants.

Overdosage of vitamin D has been associated with foetal abnormalities in animals. Animal studies have shown calcitriol to be teratogenic when given in doses 4 and 15 times the dose recommended for human use. Excessive doses of dihydrotachysterol are also teratogenic in animals. Animal studies have also shown calcifediol to be teratogenic when given in doses of 6 to 12 times the human dose.

FDA Pregnancy Category C.

Lactation:

Only small amounts of vitamin D metabolites appear in human milk. Infants who are totally breast-fed and have little exposure to the sun may require vitamin D supplementation.

Vitamin D should not be administered to patients with hypercalcaemia. It should be administered with caution to infants as they may have increased sensitivity to its effects and should be used with care in patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcaemia occurred. Plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification.

It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially and if symptoms suggest toxicity similar monitoring is recommended in infants if they are breast fed by mothers receiving vitamin D.

Growth may be arrested in children, especially after prolonged administration of 45mcg (1800 units) of colecalciferol a day.

4.7 Effects on ability to drive and use machines

Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

4.8 Undesirable effects

Note: Ingestion of excessive doses of vitamin D either as an acute overdose or over prolonged periods can result in severe toxicity.

Chronic vitamin D-induced hypercalcaemia may result in generalised vascular calcification, nephrocalcinosis, and other soft tissue calcification that may lead to hypertension and renal failure. These effects are more likely to occur when the hypercalcaemia is accompanied by hyperphosphataemia.

Growth may be arrested in children, especially after prolonged administration of 45mcg (1800 units) of colecalciferol per day.

Death may occur as a result of renal or cardiovascular failure caused by vitamin D toxicity.

Dosage necessary to cause toxicity varies with individual sensitivity, but in individuals without malabsorption problems, 250mcg (10,000 units) a day for more than several weeks or months is the maximum dose.

Toxicity may occur with therapeutic doses of calcitriol.

The following side / adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate) – not necessarily inclusive.

Those indicating need for medical attention

Early symptoms of vitamin D toxicity associated with hypercalcaemia

Constipation – usually more frequent in children and adolescents; diarrhoea; dryness of mouth; headache, continuing; increased thirst; increase in frequency of urination, especially at night, or in amount of urine; loss of appetite; metallic taste; nausea or vomiting – usually more frequent in children and adolescents; unusual tiredness or weakness.

Late symptoms of vitamin D toxicity associated with hypercalcaemia

Bone pain; cloudy urine; high blood pressure; increased sensitivity of eyes to light or irritation of eyes; irregular heartbeat; itching of skin; lethargy (drowsiness); muscle pain; nausea or vomiting and pancreatitis (stomach pain, severe); psychosis, overt (mood or mental changes);

- rare; weight loss.

The following reactions have been reported as causally related to vitamin D intake: face oedema, genital oedema, pruritus, dry skin, nail disorder, erythematosus rash, decreased prothrombin (drug interaction), purpuric rash, choking, and dysphagia. The decreased prothrombin was assessed as severe and as arising due to a possible interaction of Vitamin D with warfarin and calcium carbonate.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

Excessive intake of vitamin D leads to the development of hypercalcaemia and its associated effects including hypercalciuria, ectopic calcification, and renal and cardiovascular damage. Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, diarrhoea, polyuria, sweating headache, thirst and vertigo. Inter-individual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects.

Recommended treatment includes the following:

Hypervitaminosis D is treated by withdrawal of the vitamins, low-calcium diet, and generous fluid intake.

If hypercalcaemia persists, a low-calcium diet and prednisone may be started. Severe hypercalcaemia may be treated with calcitonin, etidronate, pamidronate, or gallium nitrate.

Hypercalcaemic crisis requires vigorous hydration with intravenous saline to increase calcium excretion, with or without a loop diuretic.

Cardiac arrhythmias may be treated with small doses of potassium with continuous cardiac monitoring.

Therapy may be reinstituted at a lower dose when serum calcium concentrations return to normal. Serum or urinary calcium levels should be obtained twice weekly after dosage changes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues, ATC code: A11CC05

Colecalciferol is a vitamin D compound which possesses the property of preventing or treating rickets.

Vitamin D is essential for promoting absorption and utilisation of calcium and phosphate and for normal calcification of bone. Along with parathyroid hormone and calcitonin, it regulates serum calcium concentrations by increasing serum calcium and phosphate concentrations as needed. Vitamin D stimulates calcium and phosphate absorption from the small intestine and mobilises calcium from bone.

Colecalciferol is transferred to the liver where it is converted to calcifediol (25-hydroxycolecalciferol), which is then transferred to the kidneys and converted to calcitriol (1,25-dihyroxycolecalciferol, thought to be the most active form) and 24,25-dihydroxycolecalciferol (physiologic role not determined).

Calcitriol appears to act by binding to a specific receptor in the cytoplasm of the intestinal mucosa and subsequently being incorporated into the nucleus, probably leading to formation of the calcium-binding protein which results in increased absorption of calcium from the intestine. Also, calcitriol may regulate the transfer of calcium ion from bone and stimulate reabsorption of calcium in the distal renal tubule, thereby effecting calcium homeostasis in the extracellular fluid.

Onset of action – Hypercalcaemic: 12 to 24 hours; therapeutic effect may take 10 to 14 days.

Duration of action – Following oral administration: up to 6 months; repeated doses have a cumulative action.

5.2 Pharmacokinetic properties

Vitamin D substances are well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption; absorption may be decreased in patients with decreased fat absorption.

Vitamin D and its metabolites circulate in the blood bound to a specific alpha-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Ergocalciferol and colecalciferol have a slow onset and a long duration of action; calcitriol and its analogue alfacalcidol, however, have a more rapid action and shorter half-lives.

Colecalciferol and ergocalciferol are hydroxylated in the liver by the enzyme vitamin D 25-hydroxylase to form 25-hydroxycolecalciferol (calcifediol) and 25-hydroxyergocalciferol respectively. These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D 1-hydroxylase to form the active metabolites 1,25-dihydroxycolecalciferol (calcitriol) and 1,25-dihydroxyergocalciferol respectively. Further metabolism also occurs in the kidneys, including the formation of the 1,24,25-trihydroxy derivatives. Of the synthetic analogues, alfacalcidol is converted rapidly in the liver to calcitriol, and dihydrotachysterol is hydroxylated, also in the liver, to its active form 25-hydroxydihydrotachysterol.

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. Certain vitamin D substances may be distributed into breast milk.

5.3 Preclinical safety data

Studies with calcitriol have found no evidence of mutagenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell: Gelatin BP, Glycerin BP, Purified water BP
Capsule fill: Refined Soya Oil BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE bottle: 36 Months
Blister pack: 36 Months

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

HDPE bottle with child resistant closure and silica desiccant. Pack-size of 12 soft gelatin capsules.

PVC/Aluminium blisters in a carton. Pack-size of 12 soft gelatin capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Multichem NZ Limited
8 Apollo Drive
Rosedale
Auckland 0632
Telephone: (09) 488 0330

9. DATE OF FIRST APPROVAL

17 February 2014

10. DATE OF REVISION OF THE TEXT

06 Apr 2018

SUMMARY TABLE OF CHANGES

DATE	CHANGE
06 Apr 2018	Update to shelf life.