For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

SHELCAL-CT MAX

1. Generic Name

Calcitriol, Omega-3 Fatty Acids, Methylcobalamin, Folic Acid, Boron, Calcium Carbonate Soft Gelatin Capsules

2. Qualitative and quantitative composition

Each soft gelatin capsule contains:

Calcitriol I.P. ……..0.25 mcg

Fish Oil, Rich in Omega-3 Fatty Acids B.P. containing

Eicosapentaenoic Acid (EPA)……180 mg

Docosahexaenoic Acid (DHA)…...120 mg

Methylcobalamin I.P. ……1500 mcg

Folic Acid I.P. …….400 mcg

Boron (as Disodium Tetraborate U.S.P.)…..1.5 mg

Calcium Carbonate I.P. ……...500 mg

Approved colours used in capsule shell.

Appropriate overages of vitamins added to compensate for loss on storage.

The excipients used are Hydrogenated vegetable oil, Bees wax, Soyalecithin, Aerosil, Butylated Hydroxy Toluene, Butylated Hydroxy Anisole, Gelatin, Glycerin, Sorbitol, Methyl Paraben, Propyl Paraben, Ponceau 4R and Titanium Dioxide.

3. Dosage form and strength

Dosage form: Soft gelatin capsule

Strength: Calcitriol 0.25 mcg, Omega-3 Fatty Acids (Eicosapentaenoic Acid (EPA)……180 mg & Docosahexaenoic Acid (DHA)…...120 mg), Methylcobalamin 1500 mcg, Folic Acid 400 mcg, Boron 1.5 mg and Calcium Carbonate 500 mg.

4. Clinical particulars

4.1 Therapeutic indication

SHELCAL-CT MAX capsule treats low blood calcium levels in people who do not get enough calcium from their diets. It is used for the treatment and prevention of conditions caused by calcium, Methylcobalamin and Folic Acid deficiency. It is used to prevent or treat low blood calcium levels in people who do not get enough calcium from their diets.

4.2 Posology and method of administration

Posology

Dose: The daily recommended dose is as directed by the Physician.

Method of administration

SHELCAL-CT MAX soft gelatin capsules should be administered orally. Do not open or crush or chew the capsule. Swallow as a whole.

4.3 Contraindications

- Hypersensitivity to any of the active substance.
- Diseases and/or conditions resulting in hypercalcemia and/or hypercalciuria, for example in hyperparathyroidism, vitamin D overdosage, decalcifying tumours such as plasmacytoma and skeletal metastases, in severe renal failure untreated by renal dialysis and in osteoporosis due to immobilisation.
- Renal calculi (nephrolithiasis).
- If there is evidence of vitamin D toxicity.
- Long-term folate therapy iscontraindicated in any patient with untreated cobalamin deficiency. This can be untreated pernicious anaemia or other cause of cobalamin deficiency, including lifelong vegetarians. In elderly people, a cobalamin absorption test should be done before long-term folate therapy. Folate given to such patients for 3 months or longer has precipitated cobalamin neuropathy. No harm results from short courses of folate.
- Folic acid should never be given alone in the treatment of Addisonian pernicious anaemia and other vitamin B_{12} deficiency states because it may precipitate the onset of subacute combined degeneration of the spinal cord.
- Folic acid should not be used in malignant disease unless megaloblastic anaemia owing to folate deficiency is an important complication.

4.4 Special warnings and precautions for use

Calcitriol

There is a close correlation between treatment with calcitriol and the development of hypercalcaemia.

All other vitamin D compounds and their derivatives, including proprietary compounds or foodstuffs which may be "fortified" with vitamin D, should be withheld during treatment with Calcitriol.

An abrupt increase in calcium intake as a result of changes in diet (e.g. increased consumption of dairy products) or uncontrolled intake of calcium preparations may trigger hypercalcaemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognise the symptoms of hypercalcaemia.

As soon as the serum calcium levels rise to 1 mg/100 ml (250 μmol/l) above normal (9-11 mg/100 ml or 2250-2750 μmol/l), or serum creatinine rises to >120 μmol/l, treatment with Calcitriol should be stopped immediately until normocalcaemia ensues.

Immobilised patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcaemia.

Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphataemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. In such cases, the plasma phosphate level should be maintained at the normal level (2-5 mg/100 ml or 0.65-1.62 mmol/l) by the oral administration of appropriate phosphate-binding agents and low phosphate diet.

The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dl^2.

Patients with vitamin D-resistant rickets (familial hypophosphataemia) who are being treated with Calcitriol must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by Calcitriol should be taken into account since this effect may modify the need for phosphate supplementation.

Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with Calcitriol, thereby ensuring that the development of hypervitaminosis D is avoided.

If the patient is switched from a long acting vitamin D preparation (e.g. ergocalciferol (vitamin D_2) or colecalciferol) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value, thereby increasing the risk of hypercalcaemia.

Patients with normal renal function who are taking Calcitriol should avoid dehydration. Adequate fluid intake should be maintained.

In patients with normal renal function, chronic hypercalcaemia may be associated with an increase in serum creatinine.

Calcitriol capsules contain sorbitol. Patients with rare hereditary problems of fructose intolerance should not take Calcitriol capsules.

Omega-3 Fatty Acids

Warnings

Because of the moderate increase in bleeding time (with the high dosage, i.e. 4 capsules), patients receiving anticoagulant therapy must be monitored and the dosage of anticoagulant adjusted if necessary. Use of this medication does not eliminate the need for the surveillance usually required for patients of this type.

Make allowance for the increased bleeding time in patients at high risk of haemorrhage (because of severe trauma, surgery, etc).

In the absence of efficacy and safety data, use of this medication in children and adolescents is not recommended.

During treatment with Omega-3 Fatty Acids, there is a fall in thromboxane A2 production. No significant effect has been observed on the other coagulation factors. Some reported studies with omega-3-acids demonstrated a prolongation of bleeding time, but the bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes.

Clinical data reported regarding the use of Omega-3 Fatty Acids in elderly patients over 70 years of age are limited.

Only limited information regarding the use in patients with renal impairment is available.

In reported studies some patients a small but significant increase (within normal values) in ASAT and ALAT was reported, but there are no data indicating an increased risk for patients with hepatic impairment. ALAT and ASAT levels should be monitored in patients with any signs of liver damage (in particular with the high dosage, i.e. 4 capsules).

Omega-3 Fatty Acids is not indicated in exogenous hypertriglyceridaemia (type 1 hyperchylomicronaemia). There is only limited experience in secondary endogenous hypertriglyceridaemia (especially uncontrolled diabetes).

There is no experience regarding hypertriglyceridaemia in combination with fibrates.

Methylcobalamin

- Methylcobalamin should not be used aimlessly for more than one month unless it is effective.
- The prolonged use of larger doses of methylcobalamin is not recommended for patients whose occupation requires the handling of mercury or mercury compounds.
- Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with Vitamin B12 suffered severe and swift optic atrophy.
- Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with Vitamin B12. Folic acid is not a substitute for Vitamin B12 although it may improve Vitamin B12-deficient megaloblastic anemia. Exclusive use of folic acid in treating Vitamin B12- deficient megaloblastic anemia could result in progressive and irreversible neurologic damage.
- Anaphylactic shock and death have been reported after parenteral Vitamin B12 administration.
- Blunted or impeded therapeutic response to Vitamin B12 may be due to such conditions as infection, uremia, drugs having bone marrow suppressant properties such as chloramphenicol, and concurrent iron or folic acid deficiency.

  <u>Precautions</u>

- Doses of Vitamin B12 exceeding 10 mcg daily may produce hematologic response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.
- The validity of diagnostic Vitamin B12 or folic acid blood assays could be compromised by medications, and this should be considered before relying on such tests for therapy.

- Vitamin B12 is not a substitute for folic acid and since it might improve folic acid deficient megaloblastic anemia, indiscriminate use of Vitamin B12 could mask the true diagnosis.
- Hypokalemia and thrombocytosis could occur upon conversion of severe megaloblastic to normal erythropoiesis with Vitamin B12 therapy. Therefore, serum potassium levels and the platelet count should be monitored carefully during therapy.
- Vitamin B12 deficiency may suppress the signs of polycythemia vera. Treatment with Vitamin B12 may unmask this condition.
- The dosing of methylcobalamin nasal spray and other intranasal medications should be separated by several hours, and these patients should have more frequent monitoring of vitamin B12 concentrations because of the potential for erratic absorption.

Folic Acid

Patients with vitamin B12 deficiency should not be treated with folic acid unless administered with adequate amounts of hydroxocobalamin, as it can mask the condition but the subacute irreversible damage to the nervous system will continue. The deficiency can be due to undiagnosed megaloblastic anaemia including in infancy, pernicious anaemia or macrocytic anaemia of unknown aethiology or other cause of cobalamin deficiency, including lifelong vegetarians.

Caution should be exercised when administering folic acid to patients who may have folate dependent tumours.

This product is not intended for healthy pregnant women where lower doses are recommended, but for pregnant women with folic acid deficiency or women at risk for the reoccurrence of neural tube defects.

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose‑galactose malabsorption should not take this medicine.

Boron

None Stated

Calcium Carbonate

In renal insufficiency the tablets should be given only under controlled conditions for hyperphosphataemia. Caution should be exercised in patients with a history of renal calculi.

Monitoring is especially important in patients on concomitant treatment with cardiac glycosides or diuretics.

During high dose therapy and especially during concomitant treatment with vitamin D and/or medications or nutrients (such as milk) containing calcium, there is a risk of hypercalcaemia and milk-alkali syndrome (hypercalcaemia, alkalosis and renal impairment) with subsequent kidney function impairment. In these patients, serum calcium levels should be monitored and renal function should be monitored.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Drugs interactions

Calcitriol

Dietary instructions, especially concerning calcium supplements, should be strictly observed, and uncontrolled intake of additional calcium-containing preparations avoided.

Concomitant treatment with a thiazide diuretic increases the risk of hypercalcaemia. Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias.

A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it.

Magnesium-containing drugs (e.g. antacids) may cause hypermagnesaemia and should therefore not be taken during therapy with Calcitriol by patients on chronic renal dialysis.

Since Calcitriol also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphatebinding agents must be adjusted in accordance with the serum phosphate concentration (normal values: 2-5 mg/100 ml, or 0.65-1.62 mmol/l).

Patients with vitamin D-resistant rickets (familial hypophosphataemia) should continue their oral phosphate therapy.

However, possible stimulation of intestinal phosphate absorption by calcitriol should be taken into account since this effect may modify the requirement for phosphate supplements.

Bile acid sequestrants including cholestyramine and sevelamer can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

Omega-3 Fatty Acids

Oral anticoagulants: Omega-3 Fatty Acids has been given in conjunction with warfarin without haemorrhagic complications. However, the prothrombin time must be checked when Omega-3 Fatty Acids is combined with warfarin or when treatment with Omega-3 Fatty Acids is stopped.

Methylcobalamin

Persons taking most antibiotics, methotrexate and pyrimethamine invalidate folic acid and vitamin B12 diagnostic blood assays.

Folic Acid

There is a specific interaction between phenytoin and folate such that chronic phenytoin use produces folate deficiency.

Correction of the folate deficiency reduces plasma phenytoin with potential loss of seizure control. Similar but less marked relationship exist with all anti-convulsant treatments including sodium valproate, carbamazepine and the barbiturates (including phenobarbital and primidone). Sulphasalazine and triamterene also inhibit absorption.

Antibacterials - chloramphenicol and co-trimoxazole may interfere with folate metabolism.

Folic acid may interfere with the toxic and therapeutic effects of methotrexate. Methotrexate and trimethoprim are specific anti-folates and the folate deficiency caused by their prolonged use cannot be treated by Folic Acid Tablets BP.

Folate supplements enhance the efficacy of lithium therapy.

Folinic acid should be used.

Nitrous oxide anaesthesia may cause an acute folic acid deficiency.

Both ethanol and aspirin increase folic elimination.

Boron

None Stated

Calcium Carbonate

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Calcium carbonate may interfere with the absorption of concomitantly administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least two hours before, or four to six hours after, oral intake of calcium.

Hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium. Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

If a bisphosphonate is used concomitantly, this preparation should be administered at least three hours before the intake of Calcium carbonate since gastrointestinal absorption may be reduced.

The efficacy of levothyroxine can be reduced by the concurrent use of calcium, due to decreased levothyroxine absorption. Administration of calcium and levothyroxine should be separated by at least four hours.

The absorption of quinolone antibiotics may be impaired if administered concomitantly with calcium. Quinolone antibiotics should be taken two hours before or after intake of calcium.

Calcium salts may decrease the absorption of iron, zinc and strontium ranelate. Consequently, iron, zinc or strontium ranelate preparations should be taken two hours before or after calcium carbonate.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Calcitriol

Pregnancy

The safety of Calcitriol during pregnancy has not been established.

Supravalvular aortic stenosis has been produced in foetuses by near-fatal oral doses of vitamin D in pregnant rabbits. There is no evidence to suggest that vitamin D is teratogenic

in humans even at very high doses. Calcitriol should be used during pregnancy only if the benefits outweigh the potential risk to the foetus.

Lactation

It should be assumed that exogenous calcitriol passes into breast milk. In view of the potential for hypercalcaemia in the mother and for adverse reactions from Calcitriol in nursing infants, mothers may breastfeed while taking Calcitriol, provided that the serum calcium levels of the mother and infant are monitored.

Omega-3 Fatty Acids

Pregnancy

There are no adequate data from the use of Omega-3 Fatty Acids in pregnant women.

Reported studies in animals have not shown reproductive toxicity. The potential risk for humans is unknown and therefore Omega-3 Fatty Acids should not be used during pregnancy unless clearly necessary.

Lactation

There are no data on the excretion of Omega-3 Fatty Acids in animal and human milk. Omega-3 Fatty Acids should not be used during lactation.

Methylcobalamin

Pregnancy

Animal reproduction studies have not been conducted with vitamin B12. It is also not known whether vitamin B12 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B12 is an essential vitamin and requirements are increased during pregnancy.

Lactation

Vitamin B12 appears in the milk of nursing mothers in concentrations which approximate the mother's vitamin B12 blood levels.

Folic Acid

Pregnancy

There are no known hazards to the use of folic acid in pregnancy, supplements of folic acid are often beneficial.

Non-drug - induced folic acid deficiency, or abnormal folate metabolism, is related to the occurrence of birth defects and some neural tube defects. Interference with folic acid metabolism or folate deficiency induced by drugs such as anticonvulsants and some antineoplastics early in pregnancy results in congenital anomalies. Lack of the vitamin or its metabolites may also be responsible for some cases of spontaneous abortion and intrauterine growth retardation.

Lactation

Folic acid is actively excreted in human breast milk. Accumulation of folate in milk takes precedence over maternal folate needs. Levels of folic acid are relatively low in colostrum but as lactation proceeds, concentrations of the vitamin rise. No adverse effects have been observed in breast fed infants whose mothers were receiving folic acid.

Boron

None Stated

Calcium Carbonate

Pregnancy

Calcium carbonate can be used during pregnancy. Daily intake should not exceed 2500 mg of calcium as permanent hypercalcaemia has been related to adverse effects on the developing foetus.

Lactation

Calcium carbonate can be used during breast-feeding. Calcium passes into breast milk but at therapeutic doses no effects on the breastfed new-born are anticipated.

4.7 Effects on ability to drive and use machines

It may have minor or moderate influence on the ability to drive and use machines. It may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Calcitriol

The adverse reactions listed below reflect the experience from investigational studies of Calcitriol, and the postmarketing experience.

The most commonly reported adverse reaction was hypercalcaemia.

The ADRs listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Summary of ADRs Occurring in Patients Receiving Calcitriol

Body Organ Class	Frequency	Adverse reaction
Immune System Disorders	Not known	Hypersensitivity, Urticaria
Metabolism and Nutrition Disorders	Very common	Hypercalcaemia
	Uncommon	Decreased appetite
	Not known	Polydipsia, Dehydration, Weight decreased

Psychiatric Disorders	Not known	Apathy, Psychiatric disturbances
Nervous System Disorders	Common	Headache
	Not known	Muscular weakness, Sensory disturbance, Somnolence
Cardiac Disorders	Not known	Cardiac arrhythmias
Gastrointestinal Disorders	Common	Abdominal pain, Nausea
	Uncommon	Vomiting
	Not known	Constipation, Abdominal pain upper, Paralytic ileus
Skin and subcutaneous tissue disorders	Common	Rash
	Not known	Erythema, Pruritus
Musculoskeletal and Connective Tissue Disorders	Not known	Growth retardation
Renal and Urinary Disorders	Common	Urinary tract infection
	Not known	Polyuria, Nocturia
General disorders and administration site conditions	Not known	Calcinosis, Pyrexia, Thirst
Investigations	Uncommon	Blood creatinine increased

Since calcitriol exerts vitamin D activity, adverse effects may occur which are similar to those found when an excessive dose of vitamin D is taken, i.e. hypercalcaemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcaemia). Occasional acute symptoms include decreased appetite, headache, nausea, vomiting, abdominal pain or abdominal pain upper and constipation.

Because of the short biological half-life of calcitriol, pharmacokinetic investigations have shown normalisation of elevated serum calcium within a few days of treatment withdrawal, i.e. much faster than in treatment with vitamin D_3 preparations.

Chronic effects may include muscular weakness, weight decreased, sensory disturbances, pyrexia, thirst, polydipsia, polyuria, dehydration, apathy, growth retardation and urinary tract infections.

In concurrent hypercalcaemia and hyperphosphataemia of > 6 mg/100 ml or > 1.9 mmol/l, calcinosis may occur; this can be seen radiographically.

Hypersensitivity reactions including rash, erythema, pruritus and urticaria may occur in susceptible individuals.

Laboratory Abnormalities

In patients with normal renal function, chronic hypercalcaemia may be associated with a blood creatinine increase.

Post Marketing

The number of adverse effects reported from clinical use of Calcitriol over a period of 15 years in all indications is very low with each individual effect, including hypercalcaemia, occurring at a rate of 0.001 % or less.

Omega-3 Fatty Acids

The frequencies of adverse reactions are ranked according to the following : very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (< 1/10000)

System Organ Class	**Frequency**	**Adverse reaction**
Immune system disorders	Rare	hypersensitivity
Metabolism and nutrition disorders	Uncommon	hyperglycaemia, gout
Nervous system disorders	Uncommon	dizziness, dysgeusia, headache
Vascular disorders	Uncommon	hypotension
Respiratory thoracic and mediastinal disorders	Uncommon	epistaxis
Gastrointestinal disorders	Common	gastrointestinal disorders (including abdominal distension, abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, eructation, gastro-oesophageal reflux disease, nausea or vomiting)
	Uncommon	gastrointestinal haemorrhage
Hepatobiliary disorders	Rare	liver disorders (including transaminases increased, alanine aminotransferase increased and aspartate aminotransferase increased)
Skin and subcutaneous tissue disorders	Uncommon	rash
	Rare	urticarial

Methylcobalamin

Summary of safety profile

In a phase III study comparing efficacy and safety of I-VIT NS and comparator vitamin B12 nasal spray, no incidences of deaths or SAE were observed with the use of I-VIT NS. A total of 9 Adverse Events (AEs) were reported in 8 subjects (3.38%). All the AEs were considered as TEAEs (Treatment Emergent Adverse Events) and majority of TEAE's were mild in severity.

System Organ Class Preferred Term	I-VIT NS (N = 157) n (%)	Comparator (N = 80) n (%)	Overall (N = 237) n (%)
Subjects with at least one TEAE in each group	4 (2.55)	4 (5.00)	8 (3.38)
Blood and lymphatic system disorders	1 (0.64)	0 (0)	1 (0.42)
Leukopenia	1 (0.64)	0 (0)	1 (0.42)
Gastrointestinal disorders	0 (0)	1 (1.25)	1 (0.42)
Dyspepsia	0 (0)	1 (1.25)	1 (0.42)
General disorders and administration site conditions	2 (1.27)	1 (1.25)	3 (1.27)
Fatigue	1 (0.64)	0 (0)	1 (0.42)
Pyrexia	1 (0.64)	1 (1.25)	2 (0.84)
Infections and infestations	0 (0)	1 (1.25)	1 (0.42)
Upper respiratory tract infection	0 (0)	1 (1.25)	1 (0.42)
Nervous system disorders	1 (0.64)	0 (0)	1 (0.42)
Headache	1 (0.64)	0 (0) [0]	1 (0.42)
Respiratory, thoracic and mediastinal disorders	0 (0)	2 (2.50)	2 (0.84)
Cough	0 (0)	1 (1.25)	1 (0.42)
Nasal pruritus	0 (0)	1 (1.25)	1 (0.42)

Abbreviation(s): AE= adverse event; ; n = number of subjects in the specified treatment category; N = number of subjects in the specified treatment; SOC = system organ class; PT = preferred term.
Note 1: SOC and PT are coded using the MedDRA Version 22.1.
Note 2: Subjects reporting a particular adverse event for SOC/PT more than once were counted only once for that adverse event under SOC/PT.

Folic Acid

High doses of folic acid might cause abdominal cramps, diarrhea, rash, sleep disorders, irritability, confusion, nausea, stomach upset, behavior changes, skin reactions, seizures, gas, excitability, and other side effects.

There is some concern that taking too much folic acid for a long period of time might cause serious side effects. Some research suggests that taking folic acid in doses of 800-1200 mcg might increase the risk of heart attack in people who have heart problems.

Other research suggests that taking these high doses might also increase the risk of cancer such as lung or prostate cancer.

System Organ Class	Frequency	Adverse reaction
Gastrointestinal disorders	Rare (≥1/10,000 to <1/1,000)	Anorexia, nausea, abdominal distension and flatulence

Immune system disorders	Rare (≥1/10,000 to <1/1,000)	Allergic reactions, comprising erythema, rash, pruritus, urticaria, dyspnoea, and anaphylactic reactions (including shock).

Boron

None Stated

Calcium Carbonate

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000).

Body Organ Class	**Frequency**	**Adverse Reactions**
Metabolism and nutrition disorders	Uncommon	Hypercalcaemia and hypercalciuria.
	Very rare	Milk-alkali syndrome (frequent urge to urinate; continuing headache; continuing loss of appetite; nausea or vomiting; unusual tiredness or weakness; hypercalcaemia, alkalosis and renal impairment). Seen usually only in Overdose.
Gastrointestinal disorders	Rare	Constipation, dyspepsia, flatulence, nausea, abdominal pain and diarrhoea.
Skin and subcutaneous disorders	Very rare	Pruritus, rash and urticaria.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

Calcitriol

Treatment of asymptomatic hypercalcaemia

Since calcitriol is a derivative of vitamin D, the symptoms of overdose are the same as for an overdose of vitamin D. Intake of high doses of calcium and phosphate together with Calcitriol may give rise to similar symptoms. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2 / dl^2. A high calcium level in the dialysate may contribute to the development of hypercalcaemia.

Acute symptoms of vitamin D intoxication: anorexia, headache, vomiting, constipation.

Chronic symptoms: dystrophy (weakness, loss of weight), sensory disturbances, possibly fever with thirst, polyuria, dehydration, apathy, arrested growth and urinary tract infections. Hypercalcaemia ensues, with metastatic calcification of the renal cortex, myocardium, lungs and pancreas.

The following measures should be considered in treatment of accidental overdosage: immediate gastric lavage or induction of vomiting to prevent further absorption. Administration of liquid paraffin to promote faecal excretion. Repeated serum calcium determinations are advisable. If elevated calcium levels persist in the serum, phosphates and corticosteroids may be administered and measures instituted to bring about adequate diuresis.

Hypercalcaemia at higher levels (>3.2 mmol/L) may lead to renal insufficiency particularly if blood phosphate levels are normal or elevated due to impaired renal function.

Should hypercalcaemia occur following prolonged treatment, Calcitriol should be discontinued until plasma calcium levels have returned to normal. A low-calcium diet will speed this reversal. Calcitriol can then be restarted at a lower dose or given in the same dose but at less frequent intervals than previously.

In patients treated by intermittent haemodialysis, a low concentration of calcium in the dialysate may also be used. However, a high concentration of calcium in the dialysate may contribute to the development of hypercalcaemia.

Omega-3 Fatty Acids

There are no special recommendations. Treatment should be symptomatic.

Methylcobalamin

No data is available for the overdose of Methylcobalamin .

Folic Acid

Except during pregnancy and lactation, folic acid should not be given in therapeutic doses greater than 0.4 mg daily until pernicious anemia has been ruled out. Patients with pernicious anemia receiving more than 0.4 mg of folic acid daily who are inadequately treated with vitamin B12 may show reversion of the hematologic parameters to normal, but neurologic manifestations due to vitamin B12 deficiency will progress. Doses of folic acid exceeding the Recommended Dietary Allowance (RDA) should not be included in multivitamin preparations; if therapeutic amounts are necessary, folic acid should be given separately.

Boron

None Stated

Calcium Carbonate

Overdose can lead to hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, nephrolithiasis and in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death.

Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification.

Milk-alkali syndrome may still occur in patients who ingest large amounts of calcium and absorbable alkali. It is not uncommon as a cause of hypercalcaemia requiring hospitalisation. The syndrome has also been reported in a patient taking recommended doses of antacids containing calcium carbonate for chronic epigastric discomfort, and in a pregnant woman taking high, but not grossly excessive, doses of calcium (about 3 g of elemental calcium daily). Metastatic calcification can develop.

Treatment of hypercalcaemia: The treatment with calcium must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued. Treatment: rehydration, and, according to severity of hypercalcaemia, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should be considered. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed.

5. Pharmacological properties

5.1 Mechanism of Action

Calcitriol

Calcitriol is the most active known form of vitamin D_3 in stimulating intestinal calcium transport. It is normally formed in the kidneys from its immediate precursor, 25-hydroxycholecalciferol. In physiological amounts it augments the intestinal absorption of calcium and phosphate and plays a significant part in the regulation of bone mineralisation.

The defective production of calcitriol in chronic renal failure contributes to the abnormalities of mineral metabolism found in that disorder.

The biological effects of calcitriol are mediated by the vitamin D receptor, a nuclear hormone receptor expressed in most cell types and functioning as a ligand-activated transcription factor that binds to DNA sites to modify the expression of target genes.

Omega-3 Fatty Acids

The omega-3 series polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids.

Omega-3 Fatty Acids is active on the plasma lipids by lowering triglyceride levels as a result of a fall in VLDL (very low density lipoprotein), and the substance is also active on haemostasis and blood pressure.

Omega-3 Fatty Acids reduces the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis and they inhibit esterification of other fatty acids.

The increase in peroxisomes of β-oxidation of fatty acids in the liver also contributes to the fall in triglycerides, by reducing the quantity of free fatty acids available for their synthesis. The inhibition of this synthesis lowers VLDL.

Methylcobalamin

Vitamin B_{12} can be converted to coenzyme B_{12} in tissues, and as such is essential for conversion of methylmalonate to succinate and synthesis of methionine from homocysteine, a reaction which also requires folate. In the absence of coenzyme B_{12}, tetrahydrofolate cannot be regenerated from its inactive storage form, 5-methyltetrahydrofolate, and a functional folate deficiency occurs. Vitamin B also may be involved in maintaining sulfhydryl (SH) groups in the reduced form required by many SH activated enzyme systems. Through these reactions, vitamin B is associated with fat and carbohydrate metabolism and protein synthesis.

Vitamin B_{12} is crucial for neurologic function, red blood cell production, and DNA synthesis, and is a cofactor for three major reactions: the conversion of methylmalonic acid to succinyl coenzyme A; the conversion of homocysteine to methionine; and the conversion of 5-methyltetrahydrofolate to tetrahydrofolate.

Folic Acid

Folic acid is a member of the vitamin B group. Folic acid is reduced in the body to tetrahydrofolate, which is a co-enzyme for various metabolic processes including the synthesis of purine and pyrimidine nucleotides, and hence in the synthesis of DNA; it is also involved in the formation and utilisation of formate.

Boron

None Stated

Calcium Carbonate

Calcium carbonate is a basic inorganic salt that acts by neutralizing hydrochloric acid in gastric secretions. It also inhibits the action of pepsin by increasing the pH and via adsorption. Cytoprotective effects may occur through increases in bicarbonate ion (HCO_3-) and prostaglandins. Neutralization of hydrochloric acid results in the formation of calcium chloride, carbon dioxide and water. Approximately 90% of calcium chloride is converted to insoluble calcium salts (e.g. calcium carbonate and calcium phosphate).

5.2 Pharmacodynamic properties

Calcitriol

Calcitriol is a synthetic preparation of calcitriol. Oral administration of Calcitriol to patients with chronic renal failure compensates for impaired endogenous production of calcitriol which is decreased when the glomerular filtration rate falls below 30 ml/min. Consequently, intestinal malabsorption of calcium and phosphate and the resulting hypocalcaemia are improved, thereby reversing the signs and symptoms of bone disease.

In patients with established post-menopausal osteoporosis, Calcitriol increases calcium absorption, elevates circulating levels of calcitriol and reduces vertebral fracture frequency.

The onset and reversal of the effects of Calcitriol are more rapid than those of other compounds with vitamin D activity and adjustment of the dose can be achieved sooner and more precisely. The effects of inadvertent overdosage can also be reversed more readily**.**

Omega-3 Fatty Acids

Omega-3 Fatty Acids increases LDL-Cholesterol in some patients with hypertriglyceridaemia. A rise in HDL-Cholesterol is only small, significantly smaller than seen after administration of fibrates, and not consistent.

The long-term lipid-lowering effect (after more than one year) is not known. Otherwise there is no strong evidence that lowering triglycerides reduces the risk of ischaemic heart disease.

During treatment with Omega-3 Fatty Acids, there is a fall in thromboxane A2 production and a slight increase in bleeding time. No significant effect has been observed on the other coagulation factors.

In reported studies 11324 patients, with recent MI (<3 months) and receiving a recommended preventative treatment associated with a Mediterranean diet, were randomised in the GISSI-Prevenzione study in order to receive Omega-3 Fatty Acids (n=2836), vitamin E (n=2830), Omega-3 Fatty Acids + vitamin E (n=2830) or no treatment (n=2828). GISSI-P was a multicentre, randomised, open-label study performed in Italy.

The results observed over 3.5 years, with Omega-3 Fatty Acids 1g/day, have shown a significant reduction of a combined endpoint including all-cause death, non fatal MI and non fatal stroke (decrease in relative risk of 15% [2-26] p=0.0226 in patients taking Omega-3 Fatty Acids alone compared to control, and of 10% [1-18] p=0.0482 in patients taking Omega-3 Fatty Acids with or without vitamin E). A reduction of the second pre-specified endpoint criteria including cardiovascular deaths, non fatal MI and non-fatal stroke has been shown (decrease in relative risk of 20% [5-32] p=0.0082 in patients taking Omega-3 Fatty Acids alone compared to control, decrease in relative risk of 11% [1-20] p= 0.0526 in patients taking Omega-3 Fatty Acids with or without vitamin E). The secondary analysis for each component of the primary endpoints has shown a significant reduction of all cause deaths and cardiovascular deaths, but no reduction of non fatal cardiovascular events or fatal and non fatal strokes.

Methylcobalamin

Vitamin B12 is essential to growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis. Cells characterized by rapid division (e.g., epithelial cells, bone marrow, myeloid cells) appear to have the greatest requirement for Vitamin B12. Vitamin B12 can be converted to coenzyme B12 in tissues, and as such is essential for conversion of methylmalonate to succinate and synthesis of methionine from homocysteine, a reaction which also requires folate. In the absence of coenzyme B12, tetrahydrofolate cannot be regenerated from its inactive storage form, 5-methyltetrahydrofolate, and a functional folate deficiency occurs. Vitamin B12 also may be involved in maintaining sulfhydryl (SH) groups in the reduced form required by many SH-activated enzyme systems. Through these reactions, Vitamin B12 is associated with fat and carbohydrate metabolism and protein synthesis. Vitamin B12 deficiency results in megaloblastic anemia, GI lesions, and neurologic damage that begins with an inability to produce myelin and is followed by gradual degeneration of the axon and nerve head.

Clinical study summary:

A multi-centric, open-label, multiple-dose, two-arm, parallel-group study was conducted in 237 subjects (220 completed) with subclinical serum vitamin B12 level <200 pg/mL.

The proportion of subjects achieving serum vitamin B12 level >200 pg/mL at Day 14 with I-VIT NS was similar to the comparator treatment. No statistically significant difference was observed between the two treatment groups with regards to subjects achieving serum vitamin B12 level >200 pg/mL at Days 14, 21 and 28 ($p>0.05$). During the study, 5 doses of I-VIT NS were administered over period of 21 days in comparison to 9 doses of comparator treatment over the same duration.

Based on nasal sensory evaluation questionnaire score assessed immediately after IP administration at Day 14, I-VIT NS treatment was well accepted by subjects with regards to overall comfort during and after nasal instillation.

Folic Acid

Folic acid is a member of the vitamin B group which is reduced in the body to tetrahydrofolate, a co-enzyme active in several metabolic processes and produces a haemopoietic response in nutritional megaloblastic anaemias (but see warning in Section 4.4 regarding need for concomitant use of hydroxycobalamin). Folic acid is rapidly absorbed and widely distributed in body tissues. It is used in the treatment and prevention of folate deficiency states.

Boron

None Stated

Calcium Carbonate

Pharmacotherapeutic group: Mineral supplements: Calcium.

An adequate intake of calcium is of importance during growth, pregnancy and breastfeeding.

5.3 Pharmacokinetic properties

Calcitriol

Absorption

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1µg Calcitriol in healthy subjects were found within 2-6 hours.

In reported study, after a single oral dose of 0.5 mcg Calcitriol in healthy subjects, the average serum concentrations of calcitriol rose from a baseline value of 40.0 ± 4.4 pg/ml to 60.0 ± 4.4 pg/ml after two hours, and then fell to 53.0 ± 6.9 after four hours, to 50.0 ± 7.0 after eight hours, to 44 ± 4.6 after twelve hours and to 41.5 ± 5.1 pg/ml after 24 hours.

Distribution

During transport in the blood at physiological concentrations, calcitriol is mostly bound to a specific vitamin D binding protein (DBP), but also, to a lesser degree, to lipoproteins and albumin. At higher blood calcitriol concentrations, DBP appears to become saturated, and increased binding to lipoproteins and albumin occurs.

Metabolism

Calcitriol is hydroxylated and oxidised in the kidney and in the liver by a specific cytochrome P450 enzyme: CYP24A1.

Several metabolites with different degrees of vitamin D activity have been identified.

Elimination

The elimination half-life of calcitriol in plasma ranges between 5 to 8 hours. However, the pharmacological effect of a single dose of calcitriol lasts at least 4 days. The elimination and absorption kinetics of calcitriol remain linear in a very broad dose range and up to 165 μg single oral dose. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation.

Omega-3 Fatty Acids

During and after absorption, there are three main pathways for the metabolism of the omega-3 fatty acids:

- the fatty acids are first transported to the liver where they are incorporated into various categories of lipoproteins and then channelled to the peripheral lipid stores;
- the cell membrane phospholipids are replaced by lipoprotein phospholipids and the fatty acids can then act as precursors for various eicosanoids;
- the majority is oxidised to meet energy requirements.

The concentration of omega-3 fatty acids, EPA and DHA, in the plasma phospholipids corresponds to the EPA and DHA incorporated into the cell membranes.

In reported Animal pharmacokinetic studies have shown that there is a complete hydrolysis of the ethyl ester accompanied by satisfactory absorption and incorporation of EPA and DHA into the plasma phospholipids and cholesterol esters.

Methylcobalamin

Methylcobalamin and cyanocobalamin are similarly absorbed from the gastrointestinal (GI)

Absorption

A mono-centric, open-label, multiple-dose single-arm, clinical study was conducted in 12 healthy subjects. Each subject received 3 doses (6 sprays, i.e. two sprays per dose, one spray in each nostril) of I-VIT NS on Day 0, 2 and 7. The time to reach maximum serum vitamin B12 level (C_{max}: 905.387 pg/mL) was 1 hr (range: 0.083 - 4.000 hrs). The mean $AUC_{(0-12)}$ was 7870.913 hr*pg/mL.

Distribution

In the blood, vitamin B12 is bound to transcobalamin II, a specific B-globulin carrier protein, and is distributed and stored primarily in the liver and bone marrow.

Elimination

About 3-8 mcg of vitamin B12 is secreted into the GI tract daily via the bile; in normal subjects with sufficient intrinsic factor, all but about one mcg is reabsorbed. When Vitamin B12 is administered in doses which saturate the binding capacity of plasma proteins and the

liver, the unbound B12 is rapidly eliminated in the urine. Retention of B12 in the body is dose-dependent.

Folic Acid

Absorption

Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the proximal part of the small intestine. Dietary folates are stated to have about half the bioavailability of crystalline folic acid. The naturally occurring folate polyglutamates are largely deconjugated and reduced by dihydrofolate reductase in the intestine to form 5-methyltetrahydrofolate (5MTHF). Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductases.

Distribution

Via portal circulation. 5MTHF from naturally occurring folate is extensively plasma bound. The principal storage site of folate is in the liver; it is also actively concentrated in the CSF. Folate is distributed into breast milk.

Biotransformation

Therapeutically given folic acid is converted into the metabolically active form 5MTHF in the plasma and liver. There is an enterohepatic circulation for folate.

Elimination

Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folic acid is removed by haemodialysis.

Boron

None Stated

Calcium Carbonate

Absorption

The amount of calcium absorbed through the gastrointestinal tract is approximately 30% of the swallowed dose.

Distribution and biotransformation

99% of the calcium in the body is concentrated in the hard structure of bones and teeth. The remaining 1% is present in the intra- and extracellular fluids. About 50% of the total blood-calcium content is in the physiologically active ionised form with approximately 10% being complexed to citrate, phosphate or other anions, the remaining 40% being bound to proteins, principally albumin.

Excretion and elimination

Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Calcitriol

In reported subchronic toxicity studies in rats and dogs indicated that calcitriol at an oral dose of 20 ng/kg/day (twice the usual human dosage) for up to 6 months produced no or minimal adverse effects. A dose of 80 ng/kg/day (8 times the usual human dosage) for up to 6 months produced moderate adverse effects; changes seen appeared to be primarily the result of prolonged hypercalcaemia.

In reported reproductive toxicity studies in rats indicated that oral doses up to 300 ng/kg/day (30 times the usual human dose) did not adversely affect reproduction. In rabbits, multiple foetal abnormalities were observed in two litters at an oral maternally toxic dose of 300 ng/kg/day and one litter at 80 ng/kg/day, but not at 20 ng/kg/day (twice the usual human dose). Although there were no statistically significant differences between treated groups and controls in the numbers of litters or foetuses showing abnormalities, the possibility that these findings were due to calcitriol administration could not be discounted.

Omega-3 Fatty Acids

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. In addition non-clinical literature data on safety pharmacology are indicating that there is no hazard for humans.

Methylcobalamin

The toxicological studies performed on the rats and rabbits demonstrated Methylcobalamin intra nasal formulation was well tolerated up to the highest tested concentration of 5000 µg/mL, which delivered 91.5 µg/kg (250 µg/day) and 189.4 µg/kg (50 µg/day) dose to rabbit and rat, respectively. A dose of 91.5 µg/kg for rabbit and 189.4 µg/kg to rats was equivalent to 3.5 times and 3.7 time the human dose of nasal spray, which was also established as NOAEL (No-Observed-Adverse-Effect-Level) for these species. At the end of study, microscopic evaluations of nasal cavity did not reveal any changes up to the highest dose of methylcobalain tested in both species.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential have not been performed.

Folic Acid

No preclinical data of relevance available

Boron

None Stated

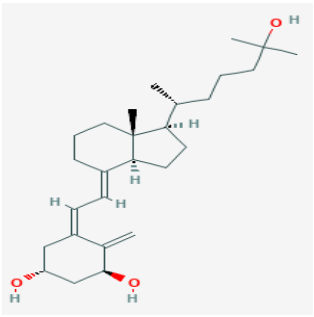
Calcium Carbonate

There is no information of relevance to the safety assessment.

7. Description

Calcitriol

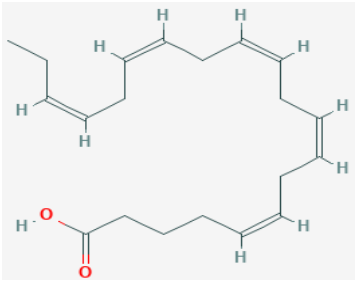
Calcitriol is a synthetic physiologically-active analog of vitamin D, specifically the vitamin D_3 form. It is chemically, (1*R*,3*S*,5*Z*)-5-[(2*E*)-2-[(1*R*,3*aS*,7*aR*)-1-[(2*R*)-6-hydroxy-6-methylheptan-2-yl]-7*a*-methyl-2,3,3*a*,5,6,7-hexahydro-1*H*-inden-4-ylidene]ethylidene]-4-methylidenecyclo hexane-1,3-diol with molecular weight of 416.6 g/mol and empirical formula is $C_{27}H_{44}O_3$. The chemical structure is:



Omega-3 Fatty Acids

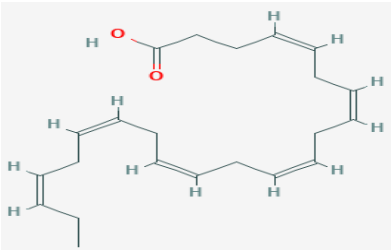
Eicosapentaenoic Acid

Eicosapentaenoic Acid is chemically, (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenoic acid with molecular weight of 302.5 g/mol and empirical formula is $C_{20}H_{30}O_2$. The chemical structure is:



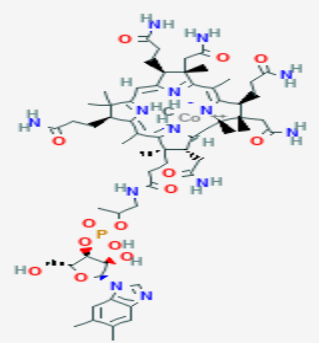
Docosahexaenoic Acid

Docosahexaenoic Acid is chemically, (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid with molecular weight of 328.5 g/mol and empirical formula is $C_{22}H_{32}O_2$. The chemical structure is:



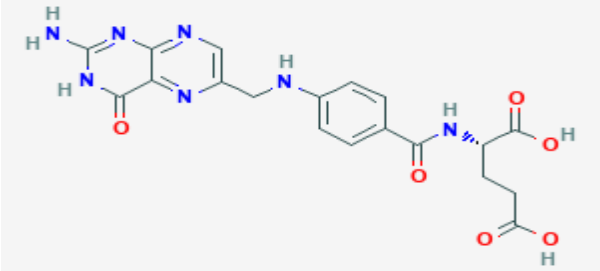
Methylcobalamin

Methylcobalamin is chemically, Coα- [α-(5,6-dimethyl-1H-benzoimidazole-1-yl)]-Coβ-methylcobamide with molecular weight of 1344.4 g/mol and empirical formula is $C_{63}H_{91}CoN_{13}O_{14}P$. The chemical structure is:



Folic Acid

Folic Acid is chemically, (2S)-2-[[4-[(2-amino-4-oxo-3H-pteridin-6-yl) methylamino]benzoyl]amino]pentanedioic acid with molecular weight of 441.4 g/mol and empirical formula is $C_{19}H_{19}N_7O_6$. The chemical structure is:



Boron

Boron is a mineral that is present naturally in the food. Boron is an element with atomic symbol B, atomic number 5, and atomic weight 10.81.

Calcium Carbonate

Calcium is a mineral that is present naturally in the food. Calcium is an element with atomic symbol Ca, atomic number 20, and atomic weight 40.08.

Calcitriol, Omega-3 Fatty Acids, Methylcobalamin, Folic Acid, Boron, Calcium Carbonate Soft Gelatin Capsules are pink and brown coloured, oblong shaped soft gelatin capsule filled with light pink coloured medicament. The excipients used are Hydrogenated vegetable oil, Bees wax, Soyalecithin, Aerosil, Butylated Hydroxy Toluene, Butylated Hydroxy Anisole, Gelatin, Glycerin, Sorbitol, Methyl Paraben, Propyl Paraben, Ponceau 4R and Titanium Dioxide.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

SHELCAL-CT MAX is packed in blister strip of 15 capsules.

8.4 Storage and handing instructions

Store in a cool, dry and dark place below 25°C. Protect from direct sunlight, heat and moisture.

Keep out of reach of children.

9. Patient counselling information

SHELCAL-CT MAX

Calcitriol, Omega-3 Fatty Acids, Methylcobalamin, Folic Acid, Boron, Calcium Carbonate Soft Gelatin Capsules

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any questions, or if there is anything you do not understand, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What SHELCAL-CT MAX is and what it is used for

9.2.What you need to know before you take SHELCAL-CT MAX

9.3.How to take SHELCAL-CT MAX

9.4.Possible side effects

9.5.How to store SHELCAL-CT MAX

9.6.Contents of the pack and other information

9.1 What SHELCAL-CT MAX is and what it is used for

SHELCAL-CT MAX is a combination of Calcitriol, Omega-3 Fatty Acids, Methylcobalamin, Folic Acid, Boron and Calcium Carbonate.

SHELCAL-CT MAX is indicated for low blood calcium levels in people who do not get enough calcium from their diets. It is used for the treatment and prevention of conditions caused by calcium, Methylcobalamin and Folic Acid deficiency. It is used to prevent or treat low blood calcium levels in people who do not get enough calcium from their diets.

9.2 What you need to know before you take SHELCAL-CT MAX

Do not take SHELCAL-CT MAX:

- If you are allergic (hypersensitive) to calcium or calcitriol or any of the other ingredients of this medicine

- Other ‘vitamin D metabolite’ medicines (used to treat bone disease). These include alfacalcidol and colecalciferol.
- have a condition that causes excessive amounts of calcium in your blood or urine (hypercalcaemia or hypercalciuria)
- have kidney stones.
- You have extra deposits of calcium in your body (metastatic calcification).
- You are unwell because of high levels of vitamin D in your body
- an untreated vitamin B12 deficiency such as in certain anaemias and lifelong vegetarians
- pernicious anaemia (a form of anaemia caused by lack of vitamin B12) or another condition caused by vitamin B12 deficiency
- a malignant (cancerous) disease.

Do not take SHELCAL-CT MAX if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking SHELCAL-CT MAX.

Warnings and precautions

Talk to your doctor or pharmacist before taking SHELCAL-CT MAX

- if you have osteoporosis (brittle bones) and are also unable to move around
- if you are on long term treatment, especially if you are taking medicines for a heart disorder (cardiac glycosides), or diuretics (used in the treatment of high blood pressure or oedema)
- if you have signs of impaired kidney function or a high tendency to kidney stone (calculus) formation
- if you have cancer or any other conditions that may have affected your bones. Your serum calcium or phosphate levels, or urinary calcium excretion must be monitored if you have any of the following conditions.
- kidney problems
- you are on long-term treatment with SHELCAL-CT MAX
- you are already taking additional doses of calcium
- If you have a folate dependent tumour
- If you are pregnant
- If you have any disease that reduces the amount of vitamin B12 in the body

If you have increased calcium levels in the blood or develop signs of kidney problems, the dose of SHELCAL-CT MAX should be reduced or the treatment discontinued.

Other medicines and SHELCAL-CT MAX

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines that you buy without a prescription and herbal

medicines. This is because SHELCAL-CT MAX can affect the way some medicines work. Also some other medicines can affect the way SHELCAL-CT MAX works.

In particular, the following medicines may interact with SHELCAL-CT MAX tablets:

- Other medicines containing vitamin D.
- **thiazide diuretics (water tablets);** your serum calcium levels should be monitored regularly.
- **cardiac glycosides (heart medicines);** Medicines like digoxin or digitoxin you should be monitored by electrocardiogram (ECG) and your serum calcium levels measured.
- **tetracycline antibiotics;** these should be taken at least two hours before, or four to six hours afterwards. Calcium carbonate may interfere with the absorption of tetracycline preparations if taken at the same time.
- **levothyroxine (hormone used to treat thyroid deficiency);** these should be taken at least four hours before, or after taking SHELCAL-CT MAX.
- **Quinolone antibiotics (ciprofloxacin, lomefloxacin, norfloxacin, sparfloxacin);** the effect of these medicines may be reduced if taken at the same time as calcium. Take quinolone antibiotics two hours before or six hours after taking SHELCAL-CT MAX.
- **Bisphosphonates** should be taken at least one hour before SHELCAL-CT MAX.
- **Calcium** salts may decrease the absorption of iron, zinc and strontium ranelate. Consequently iron, zinc or strontium ranelate preparations should be taken at least two hours before or after SHELCAL-CT MAX.
- If you are taking any of the above-mentioned medicines, your doctor will give you further instructions.
- Medicines containing magnesium, such as antacids (used to treat indigestion).
- Steroid medicines, such as hydrocortisone, prednisolone and dexamethasone.
- Cholestyramine, or other ‘ion-exchange resins’ (used to treat high levels of cholesterol in your blood).
- Phosphate (the doctor may need to monitor phosphate levels in your blood).
- antiepileptics (to treat epilepsy) such as phenytoin, phenobarbital, primidone, sodium valproate and carbamazepine
- antibacterials (to treat infections) such as trimethoprim, chloramphenicol and cotrimoxazole
- sulfasalazine (to treat ulcerative colitis, Crohn’s disease or rheumatoid arthritis)
- methotrexate (to treat Crohn’s disease, psoriasis or rheumatoid arthritis)
- lithium for mental health problems
- a gas and air mixture to put you to sleep for an operation or to relieve pain while you are awake

- alcohol
- aspirin for pain relief or to thin your blood.

Also tell your doctor or pharmacist if you have taken a medicine containing vitamin D over the last few months that has long-lasting effects. These medicines include ergocalciferol and colecalciferol.

Taking SHELCAL-CT MAX with food and drink

- Do not take any vitamin or food supplements that contain vitamin D while you are taking SHELCAL-CT MAX.
- Do not eat food which has vitamin D added (food which is 'fortified' with vitamin D) while you are taking SHELCAL-CT MAX.
- It is very important to keep to any diet that your doctor has given to you.
- If you change how much calcium or vitamin D you have in your diet this can increase the risk of side effects (for example, if you eat more dairy products like milk and cheese, or take vitamins without your doctor knowing).
- Drink plenty of fluids (such as water) as it is important not to become dehydrated. This does not apply if you have kidney problems.
- For treatment of calcium deficiency or use as an additional osteoporosis therapy, SHELCAL-CT MAX can be taken with or without food and drink.
- For use as a phosphate binder, SHELCAL-CT MAX should be taken just before, during or just after each meal.

Pregnancy, breastfeeding and fertility

Talk to your doctor before taking SHELCAL-CT MAX if you are pregnant, think you are pregnant, or plan to get pregnant. Your doctor will then decide if you should take SHELCAL-CT MAX.

During pregnancy the daily intake should not exceed 2500 mg calcium (including food and supplementation). If you are pregnant, you may use SHELCAL-CT MAX in case of a calcium deficiency.

You can take SHELCAL-CT MAX if you are breast-feeding. However, your doctor will take blood samples from you and your child to check that there are no unwanted effects.

Driving and using machines

SHELCAL-CT MAX has no known influence on the ability to drive or use machines.

9.3 How to take SHELCAL-CT MAX

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

If you take more SHELCAL-CT MAX than you should

If you have taken more SHELCAL-CT MAX than you should, talk to your doctor or pharmacist immediately.

If you accidentally take more SHELCAL-CT MAX than you should, you may have an increase in your blood calcium levels. Symptoms of this are: excessive thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, tiredness, mental disturbances, lack of appetite, bone pain, having to pass more water than usual, kidney problems and, in severe cases, irregular heartbeat.

If you take too many capsules, you may get too much calcium in your blood (hypercalcaemia). The signs include loss of appetite, weight loss, feeling sick, being sick, constipation, headache and feeling sluggish, drowsy or weak.

Very rarely in addition: irritability, continuing headache, lightheadedness, muscle spasms, twitches and tingling sensation.

If you forget to take SHELCAL-CT MAX

- If you forget to take a dose, skip the missed dose. Then take your next dose as normal.
- Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you stop taking SHELCAL-CT MAX

Do not stop taking SHELCAL-CT MAX without talking to your doctor. This is because weakness of your bones needs long term treatment.

If someone else takes your SHELCAL-CT MAX capsules by mistake, they should talk to a doctor or go to a hospital straight away.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

If you experience any of the following side effects. These side effects may be a sign of milk-alkali syndrome (also called Burnett's Syndrome) that is reported to occur very rarely (affects less than 1 in 10,000 people):

- Frequent urge to urinate
- Headache
- Loss of appetite, nausea or vomiting
- Unusual tiredness or weakness, along with elevated levels of calcium in the blood and kidney impairment.
- Side effects may include:

Uncommon side effects (may affect up to 1 in 100 people):

- excessive amounts of calcium in your blood (hypercalcaemia) or in your urine (hypercalcuria) may occur with large doses.

Rare side effects (may affect up to 1 in 1,000 people):

- nausea
- stomach ache

- constipation
- diarrhoea
- wind (flatulence)
- heartburn (dyspepsia)
- Severe allergic reaction (reaction) – anaphylactic swelling of the face, lips, tongue or throat or difficulty breathing or swallowing, shock (cold sweaty skin, weak pulse, dry mouth, dilated pupils).
- Stomach and intestines: loss of appetite, feeling sick, a bloated feeling, wind.

Very rare side effects (may affect less than 1 in 10,000 people):

- rash
- hives
- Itching

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store SHELCAL-CT MAX

Store in a cool, dry and dark place below 25°C. Protect from direct sunlight, heat and moisture light.

Keep out of reach of children

9.6 Contents of the pack and other information

What **SHELCAL-CT MAX** contains

The active substances **SHELCAL-CT MAX** is Calcitriol, Omega-3 Fatty Acids, Methylcobalamin, Folic Acid, Boron, Calcium Carbonate.

The excipients used are Hydrogenated vegetable oil, Bees wax, Soyalecithin, Aerosil, Butylated Hydroxy Toluene, Butylated Hydroxy Anisole, Gelatin, Glycerin, Sorbitol, Methyl Paraben, Propyl Paraben, Ponceau 4R and Titanium Dioxide.

10. Details of manufacturer

Manufactured in India by:

Elnova Pharma

Vill. Rampur Jattan, Moginand, Nahan Road,

Kala-Amb, Distt. Sirmour (H.P.) – 173030.

11. Details of permission or licence number with date

Mfg Lic No. MB/08/692 issued on 20.08.2018.

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/SHELCAL-CT MAX 0.25 mcg/180, 120 mg/1500 mcg/400 mcg/1.5 mg/500 mg/APR-21/01/PI