CAL360 Tablets (Calcium citrate malate + Vitamin D3)

Composition

Each film-coated tablet contains:
Calcium Citrate Malate equivalent to Elementary Calcium ... 250 mg
Cholecalciferol Concentrate (powder form) Ph. Eur. (Vitamin D3) ... 400 IU

Dosage Form

Tablet for oral use

Description

CAL360 is a fixed-dose combination of calcium citrate malate 250 mg and vitamin D3 400 IU. Calcium plays a very important role in the body. It is necessary for the normal functioning of the nerves, cells, muscle and bone. If there is not enough calcium in the blood, then the body will take calcium from bones, thereby weakening the bones. Vitamin D helps the body to absorb calcium and phosphorus. Having the right amounts of vitamin D, calcium and phosphorus is important for building and keeping strong bones.

Pharmacology

Pharmacodynamics

Calcium
Calcium plays a critical role in the body. It is essential for the normal functioning of the nerves, cells, muscle and bone. Calcium prevents bone loss and is associated with a modest reduction in fracture risk. Calcium and vitamin D preparations are used to prevent or to treat calcium deficiency. A vitamin D-resistant state may exist in uraemic patients because of the failure of the kidneys to adequately produce calcitriol.

Vitamin D3
Cholecalciferol, also called as vitamin D3, is produced naturally by ultraviolet irradiation of the provitamin, 7-dehydrocholesterol (a precursor of vitamin D) in the skin. Absorbed cholecalciferol requires metabolic activation. The circulating vitamin undergoes hydroxylation in the liver with the help of the enzyme, vitamin D 25-hydroxylase to form 25-hydroxycholecalciferol (calcidiol), which is the predominant circulating metabolite. Further hydroxylation of this metabolite in the kidneys (in response to the need for phosphorus and calcium) forms 1,25-dihydroxycholecalciferol (calcitriol), with the help of 1alpha-hydroxylase. Calcidiol possesses some intrinsic activity, but calcitriol is the most active vitamin D metabolite with respect to initiating intestinal transport of calcium and phosphate and mobilizing calcium from bone. Calcitriol may prevent phosphaturia by inhibiting parathyroid hormone (PTH) secretion. Conversion to calcitriol is stimulated by PTH as well as decreases in serum inorganic phosphate levels. Reduced renal conversion of calcidiol to calcitriol contributes to altered calcium haemostasis and osteodystrophy in uraemia.
Pharmacokinetics

Vitamin D3

Absorption
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.

Distribution
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. Cholecalciferol has a slow onset and a long duration of action.

Metabolism
Cholecalciferol is converted in the liver by hydroxylation to the active form, 25-hydroxycholecalciferol. It is then further converted in the kidneys to 1,25-dihydroxycholecalciferol. 1,25-dihydroxycholecalciferol (calcitriol) is the metabolite responsible for increasing calcium absorption. Vitamin D that is not metabolized is stored in adipose and muscle tissues.

Excretion
Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces, with only small amounts appearing in urine. There is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

Calcium

Absorption
Calcium citrate malate salt comprises 23.7% elemental calcium. In a study conducted to calculate the percent absorption of a test dose in humans, it was seen that calcium citrate malate had a mean percent absorption of 37.3%.

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

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

Indications
CAL360 is indicated for the treatment and prevention of the following:
- Calcium and vitamin D deficiency
- Calcium and vitamin D deficiency during pregnancy and lactation
- Postmenopausal osteoporosis
- Hyperphosphatemia
- Calcium and vitamin D deficiency in osteoporosis or osteomalacia

Dosage And Administration
CAL360 should be taken twice daily every week or as directed by the doctor.

Missed Dose
If the CAL360 dose is missed, the patient should be instructed to take the tablets as soon as remembered. If it is near the time of the next dose, the missed dose must be skipped and the usual dosing schedule should be resumed. Do not double the dose to catch up.

**Contraindications**

Calcium/vitamin D3 are contraindicated in the following conditions:
- Hypersensitivity to calcium citrate malate, vitamin D3 or to any of the excipients
- Hypercalcaemia
- Hypercalciuria or hypophosphatemia
- Nephrolithiasis
- Malabsorption syndrome
- Hypervitaminosis D
- Diseases and/or conditions (such as prolonged immobilization) associated with hypercalcaemia and/or hypercalciuria
- Severe renal impairment (creatinine clearance <30 ml/min).
- Renal osteodystrophy with hyperphosphataemia (risk of metastatic calcification; however, vitamin D therapy can begin once serum phosphate levels have stabilized)

**Warnings And Precautions**

**General**

Risk–benefit should be considered when the following medical problems exist:
- Vitamin D3 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 impairment, vitamin D in the form of cholecalciferol is not metabolized normally and another form of vitamin D should be used.
- During long-term treatment, serum and urinary calcium levels should be followed and renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics and in patients with a high tendency to calculus formation. Treatment must be reduced or suspended if the urinary calcium exceeds 7.5 mmol/24 hours (300 mg/24 hours). In case of hypercalcaemia or signs of impaired renal function, treatment with calcium/vitamin D3 should be discontinued.
- The dose of vitamin D3 should be considered when prescribing other drugs containing vitamin D. Additional doses of calcium or vitamin D should be taken under close medical supervision. In such cases, it is necessary to monitor serum calcium levels and urinary calcium excretion frequently. Chronic or acute administration of excessive doses may lead to hypervitaminosis D, manifested by hypercalcemia and its sequelae.
- Calcium/vitamin D3 should be used with caution in patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active metabolite. In these patients, serum calcium levels and urinary calcium excretion must be monitored.
- Calcium/vitamin D3 should be used with caution in immobilized patients with osteoporosis due to the increased risk of hypercalcaemia. The calcium/vitamin D3 treatment might be discontinued in prolonged immobilization and should only be resumed once the patient becomes mobile again.
- Conditions such as arteriosclerosis or cardiac function impairment may be exacerbated due to possibility of hypercalcaemia and elevated serum cholesterol concentrations.
Impaired calcium absorption has been observed in achlorhydria which is common in elderly. Caution should be observed in hypoparathyroid patients on high doses of vitamin D, as calcium/vitamin D3 supplement may increase the risk of hypercalcaemia and hypercalciuria. Calcium/vitamin D3 supplement should be given with caution in patients with history of kidney stones or renal failure.

Vitamin D3 should be administered with caution in patients with hyperlipidaemia as it could potentially exacerbate low-density lipoprotein (LDL) elevation. Administration of cholecalciferol in patients with hyperphosphataemia may put the patient at risk of metastatic calcification; normalization of phosphate levels is indicated prior to therapy. Liver disease may, in turn, impair the absorption of cholecalciferol.

### Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of calcitriol. Calcitriol is not mutagenic in vitro in the Ames Test, nor is it genotoxic in vivo in the Mouse Micronucleus Test. No significant effects of calcitriol on fertility and/or general reproductive performances were observed in a Segment I study in rats at doses of up to 0.3 mcg/kg (approximately 3 times the maximum recommended dose based on body surface area).

### Drug Interactions

**Vitamin D3**

**Cholestyramine**

Simultaneous treatment with ion-exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.

**Rifampicin, Phenytoin or Barbiturates**

The co-administration of phenytoin or phenobarbital will not affect plasma concentrations of vitamin D, but may reduce endogenous plasma levels of calcitriol by accelerating metabolism. Since blood level of calcitriol will be reduced, higher doses of cholecalciferol may be necessary if these drugs are administered simultaneously.

**Thiazides**

Thiazides are known to induce hypercalcaemia by the reduction of calcium excretion in urine. Some reports have shown that the concomitant administration of thiazides with vitamin D causes hypercalcaemia. Therefore, precaution should be taken when co-administration is necessary.

**Digitalis**

Vitamin D dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias.

**Ketoconazole**

Ketoconazole may inhibit both synthetic and catabolic enzymes of vitamin D. Reductions in serum endogenous vitamin D concentrations have been observed following the administration of 300 mg/day to 1,200 mg/day ketoconazole for a week to healthy men. However, in vivo drug interaction studies of ketoconazole with vitamin D have not been investigated.

**Corticosteroids**

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

**Phosphate-Binding Agents**

Since vitamin D also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration.

**Calcium Supplements**

Uncontrolled intake of additional calcium-containing preparations should be avoided.

**Magnesium**
Magnesium-containing preparations (e.g. antacids) may cause hypermagnesaemia and should, therefore, not be taken during therapy with vitamin D by patients on long-term renal dialysis.

**Vitamin D**

Since calcitriol is the most potent active metabolite of vitamin D3, pharmacological doses of vitamin D and its derivatives should be withheld during treatment with calcitriol to avoid possible additive effects and hypercalcemia.

**Calcium**

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

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose. Calcium carbonate may interfere with the absorption of concomitantly administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least 2 hours before, or 4 to 6 hours after oral intake of calcium.

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

If a bisphosphonate, sodium fluoride or fluoroquinolone is used concomitantly, these products should be administered at least 3 hours before the intake calcium/vitamin D3 since gastrointestinal absorption may be reduced.

Calcium salts may decrease the absorption of iron, zinc or strontium. Consequently, the iron, zinc or strontium preparation should be taken at a distance of 2 hours from the calcium preparation.

Calcium salts may reduce the absorption of estramustine or thyroid hormones. It is recommended that estramustine or thyroid hormones should be taken at a distance of 2 hours from the calcium preparation.

Oxalic acid (found in spinach, sorrel and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through the formation of insoluble compounds with calcium ions. The patient should not take calcium products within 2 hours of eating foods high in oxalic acid and phytic acid.

Fatal encephalopathy can occur in patients with renal failure when given calcium citrate and aluminium products concurrently due to marked rise in aluminium levels.

Use with caution in renal failure. Frequent monitoring of serum calcium, phosphorus and creatinine is needed.

**Pregnancy**

Vitamin D is likely safe during pregnancy when used in daily amounts below 4,000 units. The recommended dose of calcium during pregnancy is 1,000 mg and the upper safe limit is 2,500 mg. In pregnant women, overdoses of calcium and vitamin D should be avoided as permanent hypercalcaemia has been related to adverse effects on the developing foetus. There are no indications that vitamin D at therapeutic doses is teratogenic in humans.

**Lactation**

Calcium and vitamin D3 pass into human milk. Vitamin D is probably safe during breastfeeding when used in daily amounts below 4,000 units. The upper safe limit of calcium during lactation is 2,500 mg. Higher doses might cause serious harm to the infant.

**Paediatric Use**

The safe upper limit for vitamin D is 1,000 to 1,500 IU/day for infants, 2,500 to 3,000 IU/day for children aged 1 to 8 years, and 4,000 IU/day for children 9 years and older. The safe upper limit of calcium is 1,000 to 1,500 mg in infants; 2,500 mg in children aged 1 to 8 years and 3,000 in children aged 9 to 18 years.
Geriatric Use

Studies have shown that the elderly may have an increased need for calcium/vitamin D. However, the dose selection for an elderly patient should be cautious, usually starting at the lower end of the dose range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

Undesirable Effects

Calcium/vitamin D supplementation does not have serious side effects in most patients. Constipation or stomach upset may occur. Other side effects that may occur are nausea/vomiting, loss of appetite, unusual weight loss, mental/mood changes, change in the amount of urine, bone/muscle pain, headache, increased thirst, increased urination, weakness, swelling or tingling in mouth or throat, chest tightness, trouble breathing, tiredness and fast/pounding heartbeat. A very serious allergic reaction to this drug is rare. However, symptoms such as rash, itching/swelling (especially of the face/tongue/throat), severe dizziness and trouble breathing problem may occur. This is not a complete list of possible side effects.

Vitamin D3

Vitamin D at normal doses usually has no side effects. Too much vitamin D can cause harmful, high calcium levels. Some of the associated symptoms are nausea/vomiting, constipation, loss of appetite, increased thirst, increased urination, mental/mood changes and unusual tiredness. A very serious allergic reaction to this drug is rare. However, medical help may be needed in case of a serious allergic reaction, including rash, itching/swelling (especially of the face/tongue/throat), severe dizziness and trouble breathing. This is not a complete list of possible side effects.

Toxicity is much more likely to occur from high intakes of dietary supplements containing vitamin D. Vitamin D toxicity can cause non-specific symptoms such as anorexia, weight loss, polyuria and heart arrhythmias. More seriously, it can also raise blood levels of calcium, which leads to vascular and tissue calcification, with subsequent damage to the heart, blood vessels and kidneys. The use of supplements of both calcium (1,000 mg/day) and vitamin D (400 IU) by postmenopausal women was associated with a 17% increase in the risk of kidney stones over 7 years in the Women's Health Initiative. A serum calcidiol concentration consistently >500 nmol/L (>200 ng/mL) is considered to be potentially toxic.

Long-term intakes above the upper limit increase the risk of adverse health effects. Most reports suggest a toxicity threshold for vitamin D of 10,000 to 40,000 IU/day and serum calcidiol levels of 500 to 600 nmol/L (200 to 240 ng/mL). While symptoms of toxicity are unlikely at daily intakes below 10,000 IU/day, the FNB pointed to emerging science from national survey data, observational studies and clinical trials, suggesting that even lower vitamin D intakes and serum calcidiol levels might have adverse health effects over time. The FNB concluded that serum calcidiol levels above approximately 125 to 150 nmol/L (50 to 60 ng/mL) should be avoided, as even lower serum levels (approximately 75 to 120 nmol/L or 30 to 48 ng/mL) are associated with increases in all-cause mortality, greater risk of cancer at some sites such as the pancreas, greater risk of cardiovascular events, and more falls and fractures among the elderly. The early symptoms of vitamin D intoxication associated with hypercalcaemia include weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, flatulence, diarrhoea, ari, muscle pain and weakness, mental disturbances, anorexia, abdominal pain, thirst, nephrocalcinosis, renal calculi, bone pain and metallic taste. Late signs include polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhoea, pruritus, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolaemia, elevated SGOT and SGPT, ectopic calcification, nephrocalcinosis, hypertension, cardiac arrhythmias, dystrophy, sensory disturbances, dehydration, apathy, arrested growth, urinary tract infections and, rarely, overt psychosis.
Adverse effects are in general similar to those encountered with excessive vitamin D intake. Some uncommon disorders are hypercalcaemia and hypercalciuria. Rare incidences of constipation, flatulence, nausea, abdominal pain, diarrhoea, pruritus, rash and urticaria have also been reported. If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 18002677779 (Cipla Number) or you can report to PVPI on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

**Calcium/Vitamin D3**

Overdose can lead to hypervitaminosis, hypercalciuria and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi 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 occur in patients who ingest large amounts of calcium and absorbable alkali.

Treatment of Hypercalcaemia

The treatment with calcium must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D3 and cardiac glycosides must also be discontinued. Emptying of the stomach should be done in patients with impaired consciousness. Rehydration and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should be performed. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and central venous pressure should be undertaken.

**Storage And Handling Instructions**

Store in a cool and dry place.

**Packaging Information**

CAL360 is available in a strip pack of 10 tablets.

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