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

SHELCAL-ISO

1. Generic Name

Calcium carbonate, Calcitriol & Soya Isoflavones 40% Soft Gelatin Capsules

2. Qualitative and quantitative composition

Each soft gelatin capsule contains:

Calcium Carbonate I.P. …….500 mg

(equivalent to Elemental Calcium 200 mg)

Soya Isoflavones 40% ……60 mg

Calcitriol I.P. ……..0.25 mcg

Excipients……q.s.

Approved colours used in capsule shell.

Preservatives used Methyl Paraben I.P. & Propyl Paraben I.P.

Appropriate overages of vitamins added

The excipients used are Polysorbate 80, Colloidal Silicon Dioxide, Refined Soyabean Oil, Soyalecithin, Butylated Hydroxy Toluene, Butylated Hydroxy Anisole, Gelatin, Glycerin, Sorbitol 70%, Methyl Paraben, Propyl Paraben, Ponceau 4R, Titanium Dioxide.

3. Dosage form and strength

Dosage form: Soft gelatin capsule

Strength: Calcium Carbonate - 500 mg, Soya Isoflavones 40% 60 mg & Calcitriol 0.25 mcg

4. Clinical particulars

4.1 Therapeutic indication

SHELCAL-ISO is indicated for the clinical dietary management of the metabolic processes of osteopenia and osteoporosis.

4.2 Posology and method of administration

Posology

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

Method of administration

SHELCAL-ISO 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 the active substance.
- Diseases and/or conditions resulting in hypercalcaemia 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.

4.4 Special warnings and precautions for use

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.

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.

4.5 Drugs interactions

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.

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.

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

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.

Calcitriol

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.

It should be assumed that exogenous calcitriol passes into breast milk. In view of the potential for hypercalcemia 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.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile of reported adverse events, this product is presumed to be safe or unlikely to adversely affect such activities.

4.8 Undesirable effects

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.

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 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

System Organ Class	**Frequency**	**Adverse reaction**
Immune System	Not known	Hypersensitivity,

Disorders		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.

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

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.

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.

5. Pharmacological properties

5.1 Mechanism of Action

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).

Soya Isoflavones

Isoflavones are selective estrogen receptor modulators that exert estrogenic-like effects under certain experimental conditions, as they are structurally similar to mammalian 17β-estradiol. They may bind to both α and β isoforms of estrogen receptor (ER), but with binding affinities to ERβ approximately 20 times higher than that to ERα. The role of isoflavones on estrogen-dependent cancer has been studied, since they may mediate antiestrogenic actions by blocking the binding of endogenous estrogens and their receptor signalling

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.

5.2 Pharmacodynamic properties

Calcium Carbonate

Pharmacotherapeutic group: Mineral supplements: Calcium.

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

Soya Isoflavones

Isolated soy protein with isoflavones was shown to decrease LDL cholesterol levels in randomized trials assessed by the American Heart Association. In a reported study of postmenopausal women, daily dietary intake of 101 mg of aglycone isoflavones (indicating Genistein and Daidzein) was associated with lowered LDL cholesterol and apolipoprotein B levels by 8% and reduced systolic and diastolic blood pressure by 6.8% in hypertensive women. In a meta-analysis of randomized controlled trials of menopausal women, soy isoflavones attenuated bone loss of the spine and decreased the levels of deoxypyridinoline, a bone resorption marker, while increasing serum bone-specific alkaline phosphatase, a bone formation marker. The findings from studies investigating the effects of soy consumption on menopausal symptoms, breast cancer, and prostate cancer remain somewhat controversial and inconclusive. Consumption of soy isoflavones may decrease the markers of cancer development and progression in prostate cells, including prostate-specific antigen (PSA), testosterone, and androgen receptor in patients with prostate cancer but not in normal subjects. Although epidemiologic data in Asian women demonstrate that high soy food intake is associated with protection against breast cancer, soy foods have little effect on intermediary markers of breast cancer risk and postmenopausal soy intake may not reduce the risk of developing breast cancer 1. However, preliminary studies show that soy food intake reduces tumor recurrence in breast cancer patients. Soy isoflavones reported to interfere with thyroid peroxidase, which are involved in the production of thyroid hormones.

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**.**

5.3 Pharmacokinetic properties

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.

Soya Isoflavones

Absorption

Following oral ingestion, serum isoflavone concentrations increase in a dose-dependent manner. Isoflavones are metabolized by gut microflora, where they need to undergo deglycosylation in order to be absorbed in the intestine. After oral ingestion, glycosylated isoflavones are rapidly deglycosylated, absorbed and metabolized in intestinal enterocytes and liver, entering the systemic circulation predominantly as conjugates with limited bioavailability.

Metabolism

The conversion of glycosylated isoflavones to de-glycosylated isoflavones begins in the oral cavity, wherein oral microflora and oral epithelium exhibit β-glucosidase activity. Further conversion is mediated by intestinal lactase phlorizin hydrolase on the luminal side of the intestinal brush border to form aglycones that diffuses into the enterocytes. The glycosylated isoflavones may also be converted to aglycone in the large intestines by the resident intestinal microflora. Isoflavone aglycones that enter the intestinal cell via passive diffusion are rapidly conjugated into sulfate or glucuronide conjugates.

Elimination

Renal excretion is the predominant route of elimination for dietary isoflavones, where approximately 10-60% of total administered dose is excreted in urine. Glucuronide conjugates account for the majority (70-90%) of the isoflavone content in urine, followed by sulphate conjugates (10-25%) and aglycone forms (1-10%). Fecal excretion is minimal, which accounts for 1-4% of the dietary isoflavone ingested.

Distribution

Isoflavones are readily distributed to all tissues, and they are known to cross the placental barrier and blood brain barrier. They are also distributed to the extra-vascular compartments. In a human study, the volume of distribution of daidzein and genistein were 336.25 L and 258.76 L, respectively.

Calcitriol

Absorption

In reported studies, 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 studies 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Calcium Carbonate

There is no information of relevance to the safety assessment.

Soya Isoflavones

There is no information of relevance to the safety assessment.

Calcitriol

Subchronic reported 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 hypercalcemia.

Reproductive toxicity reported 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.

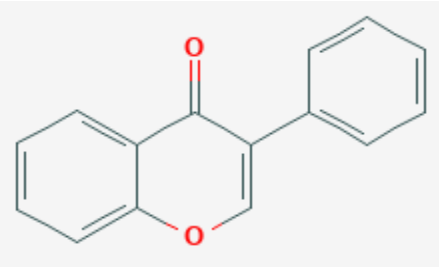
7. Description

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.

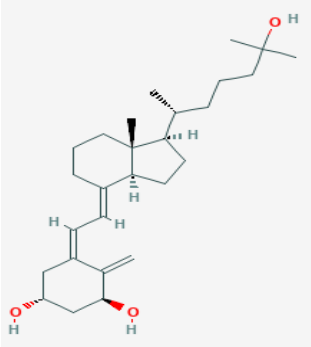
Soya Isoflavones

Soya isoflavones are polyphenols found in soy products and other plants. Isoflavone is a class of polyphenolic compounds derived from the Fabaceae family with potential phytoestrogenic, cholesterol-reducing, chemotherapeutic and antioxidant activity. It is chemically 3-phenylchromen-4-one with molecular weight of 222.24 g/mol and empiricial formula is $C_{15}H_{10}O_2$. The chemical structure is:



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:



Calcium carbonate, Calcitriol & Soya Isoflavones 40% Soft Gelatin Capsules are pink coloured, oval shaped soft gelatin capsule filled with brown coloured medicament. The excipients used are Polysorbate 80, Colloidal Silicon Dioxide, Refined Soyabean Oil, Soyalecithin, Butylated Hydroxy Toluene, Butylated Hydroxy Anisole, Gelatin, Glycerin, Sorbitol 70%, Methyl Paraben, Propyl Paraben, Ponceau 4R, 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-ISO 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 light.

Keep out of reach of children.

9. Patient counselling information

SHELCAL-ISO

Calcium carbonate, Calcitriol & Soya Isoflavones 40% 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-ISO is and what it is used for

9.2.What you need to know before you take SHELCAL-ISO

9.3.How to take SHELCAL-ISO

9.4.Possible side effects

9.5.How to store SHELCAL-ISO

9.6.Contents of the pack and other information

9.1 What SHELCAL-ISO is and what it is used for

SHELCAL-ISO is a combination of three active ingredients Calcium carbonate, Calcitriol & Soya Isoflavones.

Shelcal ISO is indicated for the clinical dietary management of the metabolic processes of osteopenia and osteoporosis.

9.2 What you need to know before you take SHELCAL-ISO

Do not take SHELCAL-ISO:

- 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

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

Warnings and precautions

Talk to your doctor or pharmacist before taking SHELCAL-ISO

- 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-ISO
- you are already taking additional doses of calcium

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

Other medicines and SHELCAL-ISO

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-ISO can affect the way some medicines work. Also some other medicines can affect the way SHELCAL-ISO works.

In particular, the following medicines may interact with SHELCAL-ISO 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-ISO.
- **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-ISO.
- **Bisphosphonates** should be taken at least one hour before SHELCAL-ISO.
- **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-ISO.
- 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).

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-ISO with food and drink

- Do not take any vitamin or food supplements that contain vitamin D while you are taking SHELCAL-ISO.
- Do not eat food which has vitamin D added (food which is 'fortified' with vitamin D) while you are taking SHELCAL-ISO.
- 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-ISO can be taken with or without food and drink.
- For use as a phosphate binder, SHELCAL-ISO should be taken just before, during or just after each meal.

Pregnancy, breastfeeding and fertility

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

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

You can take SHELCAL-ISO 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-ISO has no known influence on the ability to drive or use machines.

9.3 How to take SHELCAL-ISO

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-ISO than you should

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

If you accidentally take more SHELCAL-ISO 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-ISO

- 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-ISO

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

If someone else takes your SHELCAL-ISO 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)

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-ISO

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

Keep out of reach of children.

9.6 Contents of the pack and other information

What **SHELCAL-ISO** contains

The active substances of **SHELCAL-ISO** is Calcium Carbonate, Soya Isoflavones and Calcitriol.

The excipients used are Polysorbate 80, Colloidal Silicon Dioxide, Refined Soyabean Oil, Soyalecithin, Butylated Hydroxy Toluene, Butylated Hydroxy Anisole, Gelatin, Glycerin, Sorbitol 70%, Methyl Paraben, Propyl Paraben, Ponceau 4R, 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 14.12.2017.

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/SHELCAL-ISO 500, 60 mg, 0.25 mcg/APR-21/01/PI