Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calciup D3 500 mg/440 IU chewable tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:
1250 mg of calcium carbonate (equivalent to 500 mg of calcium).
4.4 mg of colecalciferol concentrate (powder form) (equivalent to 11 micrograms of colecalciferol = 440 IU of vitamin D3).

Excipients with known effect
Each chewable tablet contains 0.5 mg of aspartame (E951), 51.66 mg of sorbitol (E420), 185.00 mg of isomalt (E953), 0.847 mg of sucrose and 0.01 mg of benzyl alcohol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Chewable tablets.

Round, white tablets, diameter 18 mm with a faultless surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Calciup D_3 500 mg/440 IU chewable tablets are indicated:

- for the prevention and treatment of vitamin D and calcium deficiency in elderly,
- as vitamin D and calcium supplement as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency.

4.2 Posology and method of administration

The product should not be used over a period of one month without medical advice.

Posology
Adults and elderly
One chewable tablet twice daily, corresponding to a total daily dose of 1,000 mg of calcium and 880 IU of vitamin D_3

Hepatic impairment
No dose adjustment is required.

Renal impairment
Calciup D_3 500 mg/440 IU chewable tablets are contraindicated in patients with severe renal impairment (see section 4.3).

Pregnant patients
During pregnancy the daily intake should not exceed 1,500 mg of calcium and 600 I.U. of vitamin D_3. Therefore, the daily dose must not exceed one chewable tablet (see section 4.6).

Paediatric population
Calciup D_3 500 mg/440 IU chewable tablets are contraindicated in children and adolescents below 18 years of age (see section 4.3).

Method of administration
Oral use

Calciup D_3 500 mg/440 IU chewable tablets can be taken at any time, with or without food. The chewable tablets should be chewed and swallowed.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Hypercalciuria and hypercalcaemia and diseases and/or conditions, which lead to hypercalcaemia and/or hypercalciuria (e.g. myeloma, bone metastases, primary hyperparathyroidism, prolonged immobilisation accompanied by hypercalciuria and/or hypercalcaemia)
- Nephrolithiasis
- Nephrocalcinosis
- Hypervitaminosis D
- Severe renal impairment (glomerular filtration rate <30 ml/min/1.73 m^2)
- Use in children or adolescents below 18 years of age due to the high content of vitamin D in this medicinal product

4.4 Special warnings and precautions for use

During long-term treatment, serum calcium levels should be followed and renal function should be monitored through measurements of serum creatinine. Monitoring is especially important in geriatric patients on concomitant treatment with cardiac glycosides or thiazide diuretics (see section 4.5) and in patients with a high tendency to calculus formation. In case of hypercalcaemia or signs of impaired renal function, if urinary calcium excretion exceeds 300 mg/24 hours (7.5 mmoles/24 hours) the dose should be reduced or the treatment discontinued.

Calcium/colecalciferol should be used with caution in patients with hypercalcaemia or signs of impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account.

In patients with severe renal insufficiency, vitamin D in the form of cholecalciferol is not metabolised normally and other forms of vitamin D should be used (see section 4.3).

Calcium/colecalciferol should be prescribed with caution to patients suffering from sarcoidosis, due to the risk of increased metabolism of vitamin D into its active form. These patients should be monitored with regard to the calcium content in serum and urine.

Calcium/colecalciferol should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

During high dose therapy and especially during concomitant treatment with vitamin D and/or medicinal products 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 (see also section 4.8 and 4.9).
There have been literature reports alluding to possible increased absorption of aluminium with citrate salts. Calciup D_3 500 mg/440 IU chewable tablets (which contains citric acid) should be used with caution in patients with severely impaired renal function, especially in those also receiving aluminium-containing preparations.

Excipients
This medicinal product contains 0.5 mg aspartame (E951) in each tablet.
Aspartame is a source of phenylalanine. It may be harmful for patients with phenylketonuria (PKU).

This medicinal product contains 51.66 mg sorbitol (E420) in each tablet.

This medicinal product also contains isomalt (E953) and sucrose.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

This medicine contains 0.01 mg benzyl alcohol in each chewable tablet. Benzyl alcohol may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interactions

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.

Systemic corticosteroids reduce calcium absorption. Moreover the effect of vitamin D may be decreased. During concomitant use, it may be necessary to increase the dose of Calciup D_3 500 mg/440 IU chewable tablets.

Concomitant treatment with rifampicin, phenytoin or barbiturates can decrease the effect of vitamin D because of metabolic activation.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D. Therefore a time interval as long as possible between the intakes is recommended.

Orlistat may potentially impair the absorption of vitamin D as it is fat-soluble, it is advisable to not take vitamin D within 2 hours before or after orlistat administration.

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

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 and vitamin D. Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

If a bisphosphonate or sodium fluoride is used concomitantly, this preparation should be administered at least three hours before the intake of Calciup D_3 500 mg/ 440 IU chewable tablets 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 six hours after intake of calcium.

Calcium salts may decrease the absorption of iron, zinc or strontium. For this reason, iron, zinc or strontium preparations should be administered at least two hours after oral intake of calcium.

Calcium salts may reduce the absorption of the estramustin. It is advised to take this medicinal product two hours before or after such medicinal products are administered.

4.6 Fertility, pregnancy and lactation

Pregnancy
Calciup D_3 500 mg/ 440 IU chewable tablets can be used during pregnancy in case of a calcium and vitamin D deficiency. During pregnancy the daily intake should not exceed 1,500 mg of calcium and 600 I.U. of vitamin D_3. Therefore, the daily dose must not exceed one chewable tablet.

High doses of vitamin D have been shown to have teratogenic effects in animal experiments.

In pregnant women, overdoses of calcium and vitamin D should be avoided, since prolonged hypercalcaemia has been sometimes associated with retardation of physical and mental development, supravalvular aortic stenosis and retinopathy in the child.

Breast-feeding
Calciup D_3 500 mg/ 440 IU chewable tablets can be used during breast-feeding. Calcium and vitamin D_3 pass into the breast-milk. This should be considered when giving additional vitamin D to the child.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Calciup D_3 500 mg/ 440 IU chewable tablets have no or negligible influence on the ability to drive and use machines..

4.8 Undesirable effects

Summary of the safety profile:
The medicinal product may cause hypersensitivity reactions including rash, pruritis, urticaria and other systemic allergic reactions including anaphylactic reaction, face oedema, angioneurotic oedema. Uncommon cases of hypercalcaemia, hypercalciuria have been observed and rare cases of gastrointestinal disorders such as nausea, diarrhoea, abdominal pain, constipation, flatulence, abdominal distension and vomiting have been reported.

All adverse reactions are listed by system organ class and frequency which is defined as follows:

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)

Tabulated list of adverse reactions:

System Organ Class Frequency	**Adverse Reactions**
Immune system disorders Rare	hypersensitivity reactions such as angioedema or laryngeal oedema
Metabolism and nutrition disorders Uncommon Very rare	hypercalcaemia, hypercalciuria milk-alkali syndrome (Burnett-Syndrome, frequent urge to urinate, continuing headache, continuing loss of appetite, nausea or vomiting, unusual tiredness or weakness, hypercalcaemia, alkalosis and renal impairment, usually in case of overdose, see section 4.4 and 4.9)
Gastrointestinal disorders Rare	nausea, vomiting, diarrhoea, abdominal pain, constipation, flatulence, abdominal distension
Skin and subcutaneous tissue disorders Rare	Skin rash, pruritus, urticaria

Special patient group
Renal impairment
Patients with renal impairment are at increased risk for hyperphosphataemia, nephrolithiasis and nephrocalcinosis (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Symptoms
Overdose can lead to hypervitaminosis, hypercalciuria and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, dehydration, 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, soft tissue calcification, vascular and organ calcification.

The milk-alkali syndrome may 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 (see also section 4.4 and 4.8).

The threshold for vitamin D intoxication is between 40,000 and 100,000 IU per day and for calcium intoxication is from supplementation in excess of 2,000 mg per day, taken for several months, in persons with normal parathyroid function.

Management
Treatment is essentially symptomatic and supportive.

In the case of intoxication, treatment should be stopped immediately and the fluid deficiency should be corrected. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued (see section 4.5).

Emptying of the stomach in patients with impaired consciousness. Where overdose requires treatment it should be via hydration, including i.v. sodium chloride solution when needed. According to severity, isolated or combined treatment with loop diuretics (e.g. furosemide, may then be used to further increase calcium excretion and to prevent volume overload), bisphosphonates, calcitonin and corticosteroids. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed. In patients with renal failure, hydration is ineffective and they should undergo dialysis. In the case of persistent hypercalcaemia, contributing factors should be excluded, e.g. vitamin A or D hypervitaminosis, primary hyperparathyroidism, malignancies, renal failure or immobilisation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium, combinations with vitamin D and/or other drugs
ATC code: A12AX

Mechanism of action
Calciup D_3 500 mg/ 440 IU chewable tablets are a fixed combination of calcium and vitamin D_3. The high calcium and vitamin D_3 concentration in each dose unit enables sufficient absorption of calcium with a limited number of doses. Vitamin D_3 is involved in calcium-phosphorus metabolism. It allows the active absorption of calcium and phosphorus from the intestine and their uptake by bone. Supplementation with calcium and vitamin D_3 corrects latent vitamin D deficiency and secondary hyperparathyroidism.

Pharmacodynamic effects
In a double-blind placebo controlled study of 18 months, including 3,270 women aged 84 ± 6 and living in nursing homes, supplemented with cholecalciferol (800 IU/day) + calcium (1.2 g/day), a significant decrease in PTH secretion has been observed. After 18 months, the results of the intent to treat analysis showed 80 hip fractures in the calcium vitamin D group and 110 hip fractures in the placebo-group (p=0.004). So in the conditions of this study, the treatment of 1,387 women prevented 30 hip fractures. After 36 months of follow-up, 137 women presented at least one hip fracture in the calcium-vitamin D group (n=1,176) and 178 in the placebo group (n=1,127) ($p \leq 0.02$).

5.2 Pharmacokinetic properties

Calcium
Absorption
30-40% of the ingested dose of calcium is absorbed, predominantly in the proximal part of the small intestine.

Distribution and biotransformation
99% of the calcium in the body is concentrated in the mineral component 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 5% being complexed to citrate, phosphate or other anions. The remaining 45% are being bound to proteins, principally albumin.

Elimination

Calcium is excreted in the urine, faeces and in sweat. Urinary excretion depends on glomerular filtration and tubular resorption.

Vitamin D_3
Absorption
Vitamin D_3 is absorbed in the intestine.

Distribution and biotransformation
Vitamin D_3 is transported by protein binding in the blood to the liver (where it undergoes the first hydroxylation to 25-hydroxycholecalciferol) and to the kidneys (second hydroxylation to 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D_3).
Non-hydroxylated vitamin D_3 is stored in muscle and adipose tissues.

Elimination
The plasma half-life is in the order of several days; vitamin D_3 is eliminated in the faeces and urine.

5.3 Preclinical safety data

Teratogenicity has been observed in animal studies at doses far higher than the human therapeutic range. No other relevant data is available that has not been mentioned elsewhere in this Summary of Product Characteristics (see sections 4.6 and 4.9).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isomalt (E953)
Xylitol
Sorbitol (E420)
Citric acid, anhydrous
Sodium dihydrogen citrate
Magnesium stearate
Carmellose sodium
Flavour Orange "CPB" (containing natural orange oil concentrate, natural/nature identical mandarine oil (contains benzyl alcohol), natural/nature identical liquid flavour tropical fruit, natural/nature identical orange oil, natural/nature identical solid flavour multifruit, mannitol (E421), maltodextrin, gluconolactone, sorbitol (E420))
Flavour Orange "CVT" (containing natural orange oil, natural mandarine oil, nature identical powder flavor orange, mannitol (E421), gluconolactone, sorbitol (E420), medium-chained triglyceride)
Aspartame (E951)
Acesulfam potassium
Sodium ascorbate
All-rac-alpha-tocopherol
Modified (maize) starch
Sucrose
Triglycerides, medium chain
Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The chewable tablets are packed in strips of laminated aluminium paper foil and inserted in a carton.

Pack sizes:
10, 20, 30, 48, 50, 90, 100 and 120 chewable tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/217/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st August 2014
Date of last renewal: 17th June 2019

10 DATE OF REVISION OF THE TEXT

November 2020