Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calciup D_3 Forte 1000mg/880 IU Chewable Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:
2,500 mg of calcium carbonate (equivalent to 1,000 mg of calcium).
8.8 mg of colecalciferol concentrate (powder form) (equivalent to 22 micrograms of colecalciferol = 880 IU of vitamin D_3).

Excipients with known effect:

Each chewable tablet contains 1.00 mg of aspartame (E951), 119.32 mg of sorbitol (E420), 370.00 mg of isomalt (E953) and 1.694 mg of sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Chewable tablet.
Round, white tablet with faultless surface and a breakmark.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Calciup D_3 Forte 1000 mg/880 IU Chewable Tablets is indicated:

- for the prevention and treatment of vitamin D and calcium deficiency in older people
- 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

Posology
Adults and elderly
1 chewable tablet daily (corresponding to 1,000 mg of calcium and 880 IU of vitamin D_3).

Hepatic impairment
No dose adjustment is required

Renal impairment
Calciup D_3 Forte 1000 mg/ 880 IU Chewable Tablets must not be used 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 half a tablet (see section 4.6).

Paediatric population
Calciup D_3 Forte 1000 mg/ 880 IU Chewable Tablets must not be used in children and adolescents below 18 years of age (see section 4.3).

Method of administration

Oral use.

Calciup D_3 Forte 1000 mg/ 880 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
- 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.

Vitamin D 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 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).

Calciup D_3 Forte 1000 mg/880 IU Chewable Tablets 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.

Calciup D_3 Forte 1000 mg/880 IU Chewable Tablets should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

The content of vitamin D (880 IU) in Calciup D_3 Forte 1000 mg/880 IU Chewable Tablets should be considered when prescribing other medicinal products containing vitamin D. Additional doses of calcium or vitamin D should be taken only under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

Co-administration with tetracyclines or quinolones is usually not recommended, or must be done with precaution (see section 4.5).

There have been literature reports alluding to possible increased absorption of aluminium with citrate salts. Calciup D_3 Forte 1000 mg/880 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.

This medicinal product contains aspartame (E951), a source of phenylalanine which may be harmful for people with phenylketonuria. It also contains sorbitol (E420), 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 Forte 1000 mg/880 IU Chewable Tablets.

Concomitant treatment with 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.

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 high in 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 Forte 1000 mg/880 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Calciup D_3 Forte 1000 mg/880 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 half a 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 Forte 1000 mg/880 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

No data are available regarding the effects of Calciup D_3 Forte 1000 mg/880 IU Chewable Tablets on the ability to drive and use machines. However, an influence is unlikely.

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 Drug Reactions**
Immune system disorders Rare Very rare	 hypersensitivity systemic allergic reactions (anaphylactic reaction, face oedema, angioneurotic oedema)
Metabolism and nutrition disorders Uncommon	 hypercalcaemia, hypercalciuria
Gastrointestinal disorders Rare	 nausea, vomiting, diarrhoea, abdominal pain, constipation, flatulence, abdominal distension
Skin and subcutaneous tissue disorders Rare	 rash, pruritus, urticaria

Special patient group
Renal impairment
Patients with renal impairment are at increased risk for hyperphosphataemia, nephrolithiasis and nephrocalcinosis.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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 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 2000 mg per day, taken for several months, in persons with normal parathyroid function.

Management

Treatment of hypercalcaemia: The treatment with calcium and vitamin D must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics (e.g. furosemide), bisphosphonates, calcitonin and corticosteroids should be considered. In patients with renal failure, hydration is ineffective and they should undergo dialysis. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed.

In the case of persistent hypercalcaemia, contributing factors should be excluded, e.g. primary hyperparathyroidism, malignancies, renal failure or immobilisation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Combination of calcium with other drugs, ATC code A12AX

Mechanism of action
Calciup D_3 Forte 1000mg/880 IU Chewable Tablets is 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 3270 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 1387 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=1176) and 178 in the placebo group (n=1127) ($p \leq 0.02$).

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% 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

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. No other relevant data is available that has not been mentioned elsewhere in the SmPC (see section 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, 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 flavour 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
Silicon dioxide, colloidal

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

For tablet container:
Keep the tablet container tightly closed in order to protect from moisture.

For strips: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The chewable tablets are available in polypropylene tablet containers with polyethylene stoppers containing a desiccant in the following package sizes:
10, 20, 28, 30, 40, 50, 56, 60, 90, 100 (bundling package 5x20) chewable tablets

The chewable tablets are available in strips of laminated aluminium paper foil in the following package sizes:
10, 20, 28, 30, 40, 48, 56, 60, 60 (bundling package 2x30), 90, 90 (bundling package 3x30), 96, 100 (bundling package 5x20) and 120 chewable tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0711/217/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 17th February 2012

Date of Last Renewal: 21st November 2016

10 DATE OF REVISION OF THE TEXT

June 2018