SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Calcium Vitamin D_3 500 mg/440 I.U. chewable tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains 500 mg calcium (as calcium carbonate) and 11 micrograms cholecalciferol (equivalent to 440 I.U. vitamin D_3) as cholecalciferol concentrate (powder form).

Excipients with known effect
Each chewable tablet contains 1.00 mg aspartame (E 951), 0.85 mg sucrose and glucose (component of 4.00 mg maltodextrin).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet

White to off-white, round, biplane tablet (diameter 16 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention and treatment of calcium and vitamin D deficiency in the elderly.

Calcium and vitamin D supplement as an adjunct to specific osteoporosis treatment of patients who are at risk of calcium and vitamin D deficiency.

4.2 Posology and method of administration

Posology

Adults and elderly
1 chewable tablet twice daily (equivalent to 1000 mg of calcium and 880 I.U. of vitamin D_3)

Special patient populations
Paediatric population
Calcium Vitamin D_3 500 mg/440 I.U. chewable tablets are not intended for use in children and adolescents.

Renal impairment
Calcium Vitamin D_3 500 mg/440 I.U. chewable tablets should not be used in patients with severe renal impairment (see section 4.3).

Hepatic impairment
No dose adjustment is required.

Method of administration
Oral. The tablet can be chewed or sucked.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Severe renal impairment (glomerular filtration rate < 30 ml/min/1.73m^2)
- Diseases and/or conditions resulting in hypercalcaemia and/or hypercalciuria
- Renal calculi (nephrolithiasis)
- Nephrocalcinosis
- Hypervitaminosis D

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 elderly patients on concomitant treatment with cardiac glycosides or 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 the dose should be reduced or the treatment discontinued.

Calcium carbonate with cholecalciferol tablets should be used with caution in patients with signs of impaired renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account.

Calcium, vitamin D and alkali intake from other sources (e.g. milk or other foods, enriched foods, or other medicinal products) should be monitored when calcium carbonate is prescribed. When high calcium doses are given together with alkaline substances such as carbonate, there is a risk of milk-alkali syndrome (Burnett syndrome) with hypercalcaemia and subsequent kidney function impairment. Calcium levels in serum should be followed and renal function should be monitored.

Calcium Vitamin D_3 500 mg/440 I.U. 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.

Calcium Vitamin D_3 500 mg/440 I.U. chewable tablets should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

Calcium carbonate is converted into soluble chlorid in the stomach and becomes bioavailable in this way. In patients with achlorhydria, the solubility may be impaired and the bioavailability may be reduced. However, bioavailability is ensured when these patients take Calcium Vitamin D_3 500 mg/440 I.U. chewable tablets with a meal.

The acid-binding properties of calcium carbonate should be considered for concomitant use of antacids.

Excipient(s)
Aspartame
Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. It may be harmful for patients with phenylketonuria (PKU).

Glucose (component of maltodextrin)
Patients with rare glucose-galactose malabsorption should not take this medicine. May be harmful to the teeth.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per chewable tablet, that is to say essentially 'sodium-free'.

Sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to the teeth.

4.5 Interaction with other medicinal products and other forms of interaction

Thiazide diuretics reduce the urinary excretion of calcium, therefore 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 2 hours before or 4-6 hours after oral intake of calcium carbonate.

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.

Systemic corticosteroids reduce calcium absorption.

Orlistat, combined 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 may reduce the activity of vitamin D3, since they increase the rate of its metabolism.

Isoniazid may reduce the effectiveness of vitamin D3 due to inhibition of the metabolic activation of cholecalciferol.

Oxalic acid (found in spinach and rhubarb) and phytic acid (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.

If a bisphosphonate or sodium fluoride is used concomitantly, this preparation should be administered at least 3 hours before the intake of Calcium Vitamin D_3 500 mg/440 I.U. 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 4 hours.

Calcium salts may reduce the absorption of estramustin. It is recommended that this medicine should be taken at least two hours before or after Calcium Vitamin D3 500 mg/440 I.U. chewable tablets.

The absorption of quinolone antibiotics may be impaired if administered concomitantly with calcium. Quinolone antibiotics should be taken 2 hours before or 6 hours after oral intake of calcium.

Calcium salts may reduce the absorption of phosphate through formation of slightly soluble salts.

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 Calcium Vitamin D_3 500 mg/440 I.U..

Vitamin D metabolites and –analogues: A co-medication is only advised in exceptional cases. Serum calcium levels should be monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy
Calcium Vitamin D_3 500 mg/440 I.U. chewable tablets can be used during pregnancy, in case of a calcium and vitamin D deficiency. During pregnancy the daily intake should not exceed 2500 mg calcium and 4000 I.U. vitamin D.
Studies in animals have shown reproductive toxicity of high doses of vitamin D (see section 5.3).
In pregnant women, overdosage 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.

Breast-feeding
Calcium Vitamin D_3 500 mg/440 I.U. chewable tablets can be used during breast-feeding. Calcium and vitamin D_3 pass into 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

Calcium Vitamin D_3 500 mg/440 I.U. chewable tablets have no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: 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) and not known (cannot be estimated from the available data).

Immune system disorders
Not known: Hypersensitivity reactions such as angioedema or laryngeal oedema.

Metabolism and nutrition disorders
Uncommon: Hypercalcaemia, 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, soft tissue calcification and renal impairment). Seen usually only in overdose (see section 4.9).

Gastrointestinal disorders
Rare: Constipation, dyspepsia, flatulence, nausea, abdominal pain, diarrhoea.

Skin and subcutaneous tissue disorders
Very rare: Pruritus, skin rash, urticaria.

Other special population

Patients with renal impairment: potential risk of hyperphosphatemia, 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 listed in Appendix V.

4.9 Overdose

Symptoms
Overdose can lead to hypercalcaemia and hypervitaminosis D. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polidipsia, 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:
Treatment is essentially symptomatic and supportive. The treatment with calcium and vitamin D must be discontinued. Treatment with thiazide diuretics and cardiac glycosides must also be discontinued (see section 4.5). Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed. Depending on the degree of hypercalcaemia and on the patient's condition, e.g. in case of oligoanuria, haemodialysis (calcium-free dialysate) may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Vitamin D_3 increases the intestinal absorption of calcium.

Administration of calcium and vitamin D_3 counteracts the increase of parathyroid hormone (PTH) which is caused by calcium deficiency and which causes increased bone resorption.

A clinical study of institutionalised patients suffering from vitamin D deficiency indicated that a daily intake of 1000 mg calcium and 800 I.U. vitamin D for six months normalised the value of the 25-hydroxylated metabolite of vitamin D_3 and reduced secondary hyperparathyroidism and alkaline phosphatases.

An 18 month double-blind, placebo controlled study including 3270 institutionalised women aged 84+/- 6 years who received supplementation of vitamin D (800 I.U./day) and calcium phosphate (corresponding to 1200 mg/day of elemental calcium), showed a significant decrease of PTH secretion. After 18 months, an "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). A follow-up study after 36 months showed 137 women with 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: Generally, 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.
Elimination: Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

Cholecalciferol
Absorption: Vitamin D_3 is easily absorbed in the small intestine.
Distribution and biotransformation: Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. Cholecalciferol is converted in the liver by hydroxylation to 25-hydroxycholecalciferol. It is then further converted in the kidneys to the active form 1,25 dihydroxycholecalciferol. 1,25 dihydroxycholecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D_3 which is not metabolised is stored in adipose and muscle tissues.
Elimination: Vitamin D_3 is excreted in faeces and urine.

5.3 Preclinical safety data

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. There is further no information of relevance to the safety assessment in addition to what is stated in other parts of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Modified (maize) starch,
Sucrose,
Sodium ascorbate,
Medium chain triglycerides,
All-rac-alpha-Tocopherol,
Silicon dioxide,
Magnesium stearate (Ph.Eur.) [vegetable],
Maize starch,
Mannitol (Ph.Eur.) (E 421),
Aspartame (E 951),
Flavour orange (containing Maltodextrin (contains glucose), Acacia gum (gum arabic)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Tablet container:
Shelf life after first opening of the tablet container: 3 months

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Tablet container (White HDPE container closed with white, tamper-evident polypropylen screw cap and aperture for desiccant insert)
Packs of 60, 90, 100 and 180 chewable tablets.

PVC/PVDC-Aluminum-Blister (white,opaque)
Packs of 10, 20, 28, 30, 50, 56, 60, 84, 90, 100, 120 and 200 chewable tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

MM/YYYY>
To be completed nationally