SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Evacal D3 1500 mg/400 iu Chewable Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:

1,500 mg of calcium carbonate (equivalent to 600 mg of calcium).

4.0 mg of colecalciferol concentrate (powder form) (equivalent to 10 micrograms of colecalciferol = 400 IU of vitamin D_3).

Excipient(s) with known effect:

Each chewable tablet contains 0.60 mg aspartame (E951), 71.00 mg sorbitol (E420), 222.00 mg isomalt (E953) and 0.805 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Chewable tablet.

Round, white tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Evacal D3 1500 mg/400 iu Chewable Tablets are indicated:

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

Posology

Adults, elderly and children over 12 years of age

2 chewable tablets daily (corresponding to 1,200 mg of calcium and 800 IU of vitamin D_3), preferably one tablet each morning and evening.

Dosage in hepatic impairment

No dose adjustment is required.

Dosage in renal impairment

Evacal D3 1500 mg/400 iu Chewable Tablets should not be used in patients with severe renal impairment (see section 4.3).

Method of administration

Oral use.

Evacal D3 1500 mg/400 iu Chewable Tablets should be taken at any time, with or without food. The chewable tablets should be chewed and swallowed.

Evacal D3 1500 mg/400 iu Chewable Tablets are not intended for use in children under 12 years.

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

Due to its high content of vitamin D the use in children under 12 years is not indicated.

4.4 Special warnings and precautions for use

Calcium and alkali intake from other sources (food, 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. Calcium levels in serum should be monitored when administering high doses of calcium carbonate.

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 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).

Evacal D3 1500 mg/400 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.

Evacal D3 1500 mg/400 iu Chewable Tablets should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

The content of vitamin D (400 IU) in Evacal D3 1500 mg/400 iu Chewable Tablets should be considered when prescribing other medicinal products containing vitamin D. Additional doses of calcium or vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

<u>Excipient(s)</u>

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).

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

Sorbitol
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Isomalt
Patients with rare hereditary problems of fructose intolerance should not take this medicine

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

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 Evacal D3 1500 mg/400 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 (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.

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 Evacal D3 1500 mg/400 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

During pregnancy, treatment with Evacal D3 1500 mg/400 iu Chewable Tablets should always be under the direction of a physician.

Evacal D3 1500 mg/400 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 1 tablet.

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

In pregnant women, overdosage 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.

Breastfeeding

During breastfeeding, treatment with Evacal D3 1500 mg/400 iu Chewable Tablets should always be under the direction of a physician.

Evacal D3 1500 mg/400 iu Chewable Tablets can be used during breast-feeding. Calcium and vitamin D_3 and its metabolites also 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

Evacal D3 1500 mg/400 iu Chewable Tablets have no influence on the ability to drive and use machines.

4.8 Undesirable effects

The evaluation of adverse reactions is based on the following definition of frequency:

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)

Immune system disorders

Not known (cannot be estimated from the available data): Hypersensitivity reactions such as angioedema or laryngeal oedema.

Metabolism and nutrition disorders

Uncommon: Hypercalcaemia, hypercalciuria.

Not known: Milk-alkali syndrome

Gastrointestinal disorders

Rare: Nausea, diarrhoea, abdominal pain, constipation, flatulence, abdominal distension.

Skin and subcutaneous tissue disorders

Rare: Rash, pruritus, 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 Yellow Card Scheme Website:

www.mhra.gov.uk/yellowcard, or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose can lead to hypervitaminosis and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death. Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification.

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. Emptying of the stomach in patients with impaired consciousness. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Calcium carbonate and colecalciferol, ATC code A12AX01

Mechanism of action

Evacal D3 1500 mg/400 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 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

Sodium dihydrogen citrate

Magnesium stearate

Carmellose sodium

Flavour tutti frutti (containing flavouring substances, maltodextrin, propylene glycol (E1520), modified (maize) starch (E1450), monosodium citrate (E331))

Silica, colloidal hydrated

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

3 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, 30, 50, 56, 60, 90, 100, 112, 120, bundling pack containing 200 (2 packs of 100) chewable tablets

The chewable tablets are available in strips of laminated aluminium paper foil in the following package sizes:

10, 20, 30, 50, 56, 60, 90, 100, 112, bundling pack containing 112 (2 packs of 56), multipack containing 112 (2 packs of 56), 120, bundling pack containing 120 (2 packs of 60), bundling pack containing 200 (2 packs of 100) chewable tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1742

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/10/2016

10 DATE OF REVISION OF THE TEXT

29/08/2023