SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Calcium /Cholecalciferol Theramex 500 mg / 2000 IU chewable tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:
Calcium carbonate equivalent to 500 mg calcium
Cholecalciferol concentrate (powder form) equivalent to 2000IU (50 microgram) cholecalciferol (vitamin D_3)

Excipients with known effect:
Each chewable tablet contains 185 mg of isomalt, 150 mg of xylitol, 39 mg of sorbitol (E420), 0.5 mg of aspartame (E951), 3.9 mg of sucrose and 5 mg of benzyl alcohol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.
Round, white tablet,
diameter 18 mm
Orange flavour

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Invented name] are indicated:

- for treatment of calcium and vitamin D deficiency

4.2 Posology and method of administration

Posology
Adults and elderly
1 chewable tablet daily (corresponding to 500 mg of calcium and 2000 IU of vitamin D_3).

The dose of vitamin D depends on the severity of the disease, desirable serum levels of 25-hydroxycolecalciferol (25(OH)D) and patient´s response to treatment. Mono preparation is necessary for dose adjustment. The dose of calcium needed depends on the dietary intake.

Alternatively, national posology recommendations in treatment of vitamin D deficiency can be followed.

After first month, lower doses may be considered, dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment.

Pediatric Population

[Invented name] are contraindicated for use in children and adolescents aged 0 – 18 years.

Dosage in hepatic impairment
No dose adjustment is required.

Dosage in renal impairment
[Invented name] should not be used in patients with severe renal impairment (glomerular filtration rate <30 ml/min/1.73 m^2) (see section 4.3).

Coadministration with HIV integrase inhibitors
For patients receiving treatment for human immunodeficiency virus (HIV) with HIV integrase inhibitor drugs (e.g., raltegravir, dolutegravir, elvitegravir) the SmPC of the particular HIV integrase inhibitor should be consulted for adequate recommendations regarding coadministration with calcium (see section 4.5)

Method of administration

Oral use.

[Invented name] should be taken at any time, with or without food. The chewable tablets should be chewed and swallowed.
Attention should be given to a sufficient daily intake of calcium by nutrition (i.e. milk products, vegetables, mineral water).

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)

Due to its high content of vitamin D the use in children or adolescents is not indicated.

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 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 urinarycalcium 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).

[Invented name] 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.

[Invented name] should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

The content of vitamin D (2000 IU) in [Invented name]should be considered when prescribing other medicinal products containing vitamin D or food supplemented with 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.

Co-administration with tetracyclines or quinolones is usually not recommended, or must be done with precaution (see section 4.5).
The calcium and alkali intake from other sources (food, dietary supplements and other drugs) should be taken into consideration when prescribing [Invented name]. High doses of calcium or vitamin D should only be given under close medical supervision. In these cases,

frequent monitoring of the calcium level in the serum and urine is necessary. If high doses of calcium are taken concomitantly with absorbable alkali agents (like carbonate) this could lead to milk-alkali syndrome (Burnett-Syndrome), i.e. hypercalcaemia, metabolic alkalosis, renal failure and soft tissue calcification.

This medicinal product contains aspartame (E951), a source of phenylalanine which may be harmful for people with phenylketonuria. Each chewable tablet 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. May be harmful to the teeth.

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

The medicinal product contains traces of benzyl alcohol. Benzyl alcohol may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

An interaction between calcium-containing products and the HIV integrase inhibitor drug class (e.g., raltegravir, dolutegravir, elvitegravir) has been reported. Coadministration of calcium and drugs of this class have been shown to result in reduced absorption and therapeutic effect of the HIV integrase inhibitor drug. In instances of necessary coadministration, the SmPC for the coadministrated HIV integrase inhibitor should be consulted for relevant recommendations (see Section 4.2)

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 [Invented name]

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

Simultaneous treatment with orlistat, ion exchange resins such as cholestyramine or laxatives such asparaffin 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 [Invented name] 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 ranelate. Consequently, the iron, zinc or strontium ranelate preparation should be taken at a distance of two hours from the calcium preparation.

Calcium salts may decrease the absorption of estramustine and simultaneous intake must therefore beavoided.

4.6 Fertility, pregnancy and lactation

Pregnancy
[Invented name] is not recommended during pregnancy in patients without a vitamin D and calcium deficiency. Where there is a vitamin D deficiency the recommended dose is dependent on national guidelines, however, the maximum daily dose should not exceed 2500 mg calcium and 4,000 IU vitamin D per day. Studies in animals have shown reproductive toxicity of high doses of vitamin D (see section 5.3). In pregnant women, overdoses 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 and vitamin D3 pass into the breast-milk and an overdose has to be avoided in the infant. Due to the high vitamin D3 content of [Invented name] a risk to the infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue [Invented name] therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Alternatively, treatment may be switched to other calcium and vitamin D3 containing medicinal products containing vitamin D3 in lower strength.

Fertility
Normal endogenous levels for calcium and vitamin D are not expected to have any adverse effects on fertility.

4.7 Effects on ability to drive and use machines

[Invented name] have no influence on the ability to drive and usemachines.

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.

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

Skin and subcutaneous tissue disorders
Rare: Rash, pruritus, urticaria.

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
[To be completed nationally]

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

[Invented name] are a fixed combination of calcium and vitamin D_3. 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.

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
Monosodium citrate
Carmellose sodium
Magnesium stearate
Flavour Orange “CPB”
Benzyl alcohol
Propylene glycol
Flavour Orange “CVT”
Mannitol
Silica, colloidal hydrated
Aspartame (E951)
Acesulfam potassium
Sodium ascorbate
All-rac-alpha-tocopherol
Modified 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 temperature storage conditions. Keep the tablet container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

The chewable tablets are available in polypropylene tubes with a polyethylene stopper containing a descant or laminated aluminium-paper-foil strips. Tear up the strip to open.

Pack sizes
Tubes: 30, 60 (2x30) and 90 (3x30) chewable tablets.
Strips: 30 (5x6), 60 (10x6) and 90 (15x6) chewable tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special 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

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

23 February 2024