# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Accrete D3 One a Day 1000 mg / 880 IU Chewable Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains

1,000 mg calcium (as calcium carbonate) and 22 micrograms cholecalciferol (vitamin $D_3$ equivalent to 880 IU as concentrate powder form).

Excipient(s) with known effect

Each chewable tablet contains 1.00 mg of aspartame (E 951), up to 152.89 mg of sorbitol (E 420), 370.00 mg of isomalt (E 953), 1.694 mg of sucrose and 0.02 mg benzyl alcohol.

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 doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Accrete D3 One a Day Chewable tablets is 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 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*

Accrete D3 One a Day 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*

Accrete D3 One a Day Chewable tablets must not be used in children and adolescents below 18 years of age (see section 4.3).

Method of administration

Oral use.

Accrete D3 One a Day 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/cholecalciferol should be used with caution in patients with increased risk of 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).

Accrete D3 One a Day 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.

Accrete D3 One a Day 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 Accrete D3 One a Day 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.

A potential additional ingestion of calcium and alkaline products (due to the intake of nutrients, fortified foods or other medicinal products) should be considered. A milk-alkali syndrome (Burnett-Syndrome), i.e. hypercalcaemia, metabolic alkalosis, renal failure and soft tissue calcification can occur if high doses of calcium are taken concomitantly with absorbable alkali medicinal products (like carbonate).

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. Accrete D3 One a Day Chewable tablets contains citric acid.

<u>Paediatric population</u>
Calcium/cholecalciferol is contraindicated in children and adolescents below 18 years (see section 4.3).

<u>Accrete D3 One a Day Chewable tablets contains sodium, aspartame, sorbitol, isomalt, sucrose and benzyl alcohol</u>

This medicinal product contains less than 1 mmol sodium (23 mg) per chewable tablet, that is to say essentially ‘sodium-free’.
This medicinal product contains 1.00 mg aspartame (E 951) in each chewable tablet. Aspartame is a source of phenylalanine which may be harmful for people with phenylketonuria.
This medicinal product contains up to 152.89 mg sorbitol (E 420) in each chewable tablet. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
It also contains isomalt (E 953) 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 0.02 mg benzyl alcohol in each chewable tablet. Benzyl alcohol may cause allergic reactions.

## 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 Accrete D3 One a Day Chewable tablets.

Concomitant treatment with rifaximin, 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 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, sodium fluoride or fluoroquinolones are used concomitantly, this preparation should be administered at least three hours

before the intake of Accrete D3 One a Day Chewable tablets since gastrointestinal absorption may be reduced.

Calcium salts may decrease the absorption of iron, zinc or strontium ranelate. Consequently, the iron, zinc or strontium ranelate preparations should be taken at a distance of two hours from the calcium preparation.

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Accrete D3 One a Day 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.

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

Accrete D3 One a Day 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

Accrete D3 One a Day Chewable tablets have no known 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**<br>Frequency | **Adverse Drug Reactions** |
|---|---|
| **Immune system disorders**<br>Not known | Hypersensitivity reactions such as angioedema or laryngeal oedema |
| **Metabolism and nutrition disorders**<br>Uncommon<br><br>Not known | hypercalcaemia, hypercalciuria<br><br>Milk-alkali syndrome (frequent urge to urinate, continuing headache, continuing loss of appetite, nausea or vomiting, unusual tiredness or weakness, hypercalcaemia, alkalosis and renal impairment). Seen usually only in overdose (see section 4.9). |
| **Gastrointestinal disorders**<br>Rare<br><br><br>Not known | nausea, diarrhoea, abdominal pain, constipation, flatulence, abdominal distension<br><br>vomiting |
| **Skin and subcutaneous tissue disorders**<br>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 Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 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 of hypercalcaemia, alkalosis and renal impairment still 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.

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 is essentially symptomatic and supportive.

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 (see section 4.5).

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.

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:
Combination of calcium with other drugs, ATC code A12AX

Mechanism of action

Accrete D3 One a Day 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 (E 953)
Xylitol
Sorbitol (E 420)
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 (E 421), maltodextrin, gluconolactone, sorbitol (E 420))

Flavour Orange “CVT” (containing natural orange oil, natural mandarine oil, nature identical powder flavour orange, mannitol (E 421), gluconolactone, sorbitol (E 420), medium-chained triglyceride)
Aspartame (E 951)
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:
After first opening:
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 or in strips of laminated aluminium paper foil.

Pack sizes:
*Bottle: 10, 20, 28, 30, 40, 50, 56, 60, 90, 100 (bundling package 5x20) chewable tablets*
*Strips: 10, 20, 28, 30, 40, 48, 56, 60, 60 (bundling package 2x30), 90, 90 (bundling package 3x30), 96, 100 (bundling package 5x20), 120 and multipack of 120 (2 packs of 60) 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

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1318

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/12/2019

## 10 DATE OF REVISION OF THE TEXT

06/11/2023