Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Caltrate 600 mg/400 IU, Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
600 mg of calcium (as calcium carbonate)
10 micrograms of cholecalciferol (equivalent to 400 I.U. vitamin D_3)

Excipients with known effect: sucrose, partially hydrogenated soya bean oil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Capsule-shaped grey/beige tablets. One side is scored and engraved with "D" on the left and "600" on the right of the score. The other side is engraved with "Caltrate".

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Correction of combined vitamin D and calcium deficiencies in older people.
Supply of vitamin D and calcium associated with specific treatments for osteoporosis:

- In patients where combined vitamin D and calcium deficiencies have been diagnosed
- Or those at high risk of such deficiency.

4.2 Posology and method of administration

Posology

For oral use.
Calcium should be provided from the diet or from other sources for additional calcium requirements.
The calcium dose should be calculated based on elemental calcium daily needs for the different ages and metabolic situations and the amount of calcium in food.
The necessary daily intake of cholecalciferol will depend on the different metabolic situations.

Adults and Older People
One tablet twice a day (e.g. one tablet in the morning and one tablet in the evening). Dose reduction should be considered as necessary following the monitoring of calcium levels as indicated in section 4.4 and 4.5.

Paediatric population
No data are available

Renal impairment
Dose adjustment may be needed (see section 4.4).
Hepatic insufficiency
The dose does not require adjustment.

Method of administration
The tablet should be swallowed with a large glass of water and taken with food.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- The product contains partially hydrogenated soya bean oil and is contraindicated for patients hypersensitive to peanut or soya.
- Renal failure.
- Hypercalciuria and hypercalcaemia.
- Kidney stones (nephrolitiasis, nephrocalcinosis) or a low-phosphate diet.
- Hypervitaminosis D.

4.4 Special warnings and precautions for use

Prolonged treatment of higher than recommended doses may result in hypercalcaemia and milk alkali syndrome, particularly in patients with renal insufficiency. In such cases, the dose should be reduced or discontinued.

Caltrate should be prescribed with caution to patients who are immobilized and suffering from osteoporosis, because of the increased risk of hypercalcaemia.

Take into account the intake of vitamin D and calcium from all other sources (other medicinal products, food, dietary supplements) before prescribing Caltrate. As this product already contains vitamin D, the additional administration of vitamin D or calcium must be carried out under strict medical supervision with regular monitoring of calcaemia and calciuria. Additional doses of calcium or vitamin D should be taken only if the expected benefits outweigh the potential risks.

Caltrate must be used with caution in patients suffering from sarcoidosis because of a possible increase in vitamin D_3 metabolism in to its active form. In these patients, calcaemia and calciuria should be monitored.

Caltrate must be used with caution and serum and urinary calcium together with phosphate levels should be monitored while on drug The risk of soft tissue calcification should be taken into account. This monitoring is particularly important in older people, in cases of combined treatment with cardiac glycosides or diuretics (see section 4.5) and in patients who are frequently subject to the formation of kidney stones. In the presence of hypercalcaemia or signs of problems with renal function, the dose should be reduced or treatment interrupted. In patients with severe renal insufficiency, vitamin D_3 in the form of cholecalciferol is not metabolised in the normal way and other forms of vitamin D_3 should be used (see section 4.3).

Post-marketing cases of asphyxiation due to tablet choking have been reported. It is always recommended to take tablets with a large glass of water (200 ml). In order to facilitate intake by patients, especially older people or patients with known difficulties in swallowing, the breakable tablet may be divided into two parts before taking them with a large glass of water.

Special warnings about excipients

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

This product contains sucrose, therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This product contains partially hydrogenated soya bean oil which can cause hypersensitivity reactions (urticaria, anaphylactic shock). It is therefore contraindicated for patients hypersensitive to peanut or soya (see section 4.3).

Paediatric population
Caltrate is not intended for use in children and adolescents. Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium salts are known to decrease the absorption of concomitantly administered drugs such as bisphosphonates, tetracyclines, sodium fluoride, fluoroquinolone and ciprofloxacin due to adsorptive mechanism or delaying of gastric emptying or alkalinisation of gastric juice. Typically, this can be avoided by giving other drugs 2-4 hours before or after the administration of calcium salts on the advice of a doctor. Always read the label of concomitant medication prior to use as some medications may contraindicate the use of calcium containing products.

Thiazide diuretics can reduce calcium excretion in the urine. Because of the increased risk of hypercalcaemia, calcium monitoring is recommended in cases when thiazide diuretics are given simultaneously.
Systemic corticosteroids reduce calcium absorption. In the case of concomitant administration of corticosteroids, it might be necessary to increase the dose of Caltrate.

Orlistat, combined ion-exchange resin treatment such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D_3. Therefore Caltrate is recommended to be taken one hour before or 4-6 hours after intake of these preparations.

Hypercalcaemia can increase the toxicity of cardiac glycosides in the case of simultaneous administration with calcium and vitamin D. Consequently patients must be monitored regularly (ECG check and calcaemia).

Phenytoin or barbiturates may reduce the activity of vitamin D_3, since they increase the rate of its metabolism.

Calcium salts may decrease the absorption of iron or zinc. Consequently, the iron or zinc preparation 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 recommended that taking Caltrate be spaced at least 2 hours from these medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of Caltrate during pregnancy is not recommended.
Animal studies have shown toxic effects on reproduction at high doses of vitamin D.
In pregnant women, overdoses of calcium and vitamin D should be avoided as persistent hypercalcemia has been related to adverse effects on the developing foetus.

Breast-feeding
The use of Caltrate during breastfeeding is not recommended. Calcium and vitamin D_3 (and its metabolites) pass into maternal milk.
Fertility
There are no data on the effects of Calcium + Vitamin D on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

.Caltrate is unlikely to have an influence on the ability todrive and use machines.

4.8 Undesirable effects

Adverse effects are listed below, classified by system, organ, class and frequency. Frequencies are 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) or not known (cannot be estimated from available data).

The following adverse reactions have been observed from during post-marketing data and therefore the frequency of these reactions cannot be accurately determined.

Gastrointestinal disorders
Rare: constipation, flatulence, nausea, belching, vomiting, abdominal pain and diarrhoea.

Skin and subcutaneous tissue disorders
Rare: pruritis, rash and urticaria.

Immune system disorders
Not known: hypersensitivity reactions including angioedema.

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, website: www.hpra.ie

4.9 Overdose

An overdose can lead to hypervitaminosis, hypercalciuria and hypercalcaemia. The symptoms of hypercalcaemia can include: anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, renal calculi, nephrocalcinosis, nephrolithiasis, and in severe cases, cardiac arrhythmia, "Burnett's syndrome". Extreme hypercalcaemia may lead to coma and death. Continuous high calcium levels may lead to irreversible damage to the kidneys and soft tissue calcification.

Treatment
All calcium and vitamin D_3 treatments must be stopped immediately, and the fluid deficiency should be corrected.
Where overdosage requires treatment, it should be via hydration, including i.v. saline solution. A loop diuretic (e.g. furosemide) may then be used to further increase calcium excretion and to prevent volume overload, but thiazide diuretics should be avoided. In patients with renal failure, hydration is ineffective, and they should undergo dialysis. In the case of persistent hypercalcemia, contributing factors should be excluded, e.g. vitamin A or D hypervitaminosis, primary hyperparathyroidism, malignancies, renal failure, or immobilization.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium carbonate and cholecalciferol, **ATC Code: A12 AX.**

Mechanism of Action
Calcium + Vitamin D is a fixed dose combination of calcium and vitamin D. Calcium has both passive and active functions. The passive functions such as activation of enzymes that play a role in digestion, in the blood-coagulation cascade, or in immune defence are little affected by changes in plasma calcium concentrations. In contrast, the active functions are very sensitive to changes in extracellular calcium levels. Therefore, calcium homeostasis is essential for the normal functioning of different body systems. Extraskeletal calcium fulfils many important active metabolic and regulatory tasks. These active functions of calcium include bone and tooth mineralisation, intracellular signalling as second messenger in many signal transduction pathways, the transmission of nerve impulses, muscle contraction, and the maintenance of endothelial and epithelial barriers.

Vitamin D is involved in calcium-phosphorus metabolism. It allows the active absorption of calcium and phosphorus from the intestine and their uptake by bone.

Clinical Studies
An 18-month, double-blind, placebo-controlled study carried out in 3270 women living in institutions, aged 84 ± 6 years and receiving a vitamin D_3 supplement (800 IU/day) and calcium phosphate (corresponding to 1200 mg/day of elemental calcium), showed a significant decrease in PTH secretion. After 18 months, following an "intention to treat" (ITT) analysis, 80 hip fractures were observed in the calcium-vitamin D_3 group and 110 hip fractures in the placebo group ($p=0.004$). In a follow-up study after 36 months, 137 women with at least one fracture of the hip were observed in the calcium-vitamin D3 group (n = 1176) versus 178 women in the placebo group (n = 1127) ($p \leq 0.02$).
Calcium and vitamin D supplementation is a well-established basis of treatment and prevention of osteoporosis. Studies have shown that ingesting an appropriate amount of calcium can increase Bone Mineral Density (BMD). A Cochrane analysis

concluded that there is high-quality evidence that supplementation with calcium and vitamin D significantly reduces the risk of hip fracture (relative risk [RR]: 0.84; 95% confidence interval [CI]: 0.74, 0.96; *P*=0.01), nonvertebral fracture (RR: 0.86; 95% CI: 0.78, 0.96; *P*=0.0058), and any fracture (RR: 0.95; 95% CI: 0.90, 0.99; *P*=0.025) in post-menopausal women and older men at risk for fractures. This is in agreement with the consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases and the International Osteoporosis Foundation (IOF), which states that supplementation with calcium and vitamin D leads to a reduction in the risk of future fracture (RR: 0.89; 95% CI: 0.81, 0.96). It was also concluded that patients in groups at high risk of inadequate dietary calcium intake, as well as those undergoing treatment for osteoporosis with bisphosphonates, derive the greatest benefit from supplementation.

Pharmacodynamic Effects:
Supplementation with calcium and vitamin D counteracts the increase of parathyroid hormone (PTH) which is caused by calcium deficiency and which causes increased bone resorption.

5.2 Pharmacokinetic properties

Calcium

*Absorption:*in the stomach, calcium carbonate releases calcium ions depending upon pH. The amount of calcium absorbed by the gastrointestinal tract (predominantly in the proximal part of the small intestine) is approximately 30-40% of the ingested dose. The bioavailability of calcium can be slightly increased by concomitant intake of food. Vitamin D is required for calcium absorption and increases the capability of the absorptive mechanisms.

*Distribution and metabolism:*99% of calcium in the body is stored in the hard matter of bones and teeth. The remaining one percent is found in intra and extracellular liquids. Approximately 50% of total blood calcium is found in the physiologically active ionised form, of which approximately 5% in complexes with citrate, phosphate or other anions with 45% remaining bound to proteins, mainly albumin.

*Elimination:*calcium is eliminated in the faeces, urine and in sweat. Kidney excretion depends on glomerular filtration and on calcium reabsorption by the tubules.

Vitamin D

Absorption: vitamin D is easily absorbed by the small intestine.

*Distribution and metabolism:*cholecalciferol and its metabolites circulate in the blood, linked to a specific alpha globulin(Vitamin D Binding Protein). Cholecalciferol is metabolised in the liver by hydroxylation to its active form, 25-hydroxycholecalciferol. It is then metabolised in the kidneys to 1,25-dihydroxycholecalciferol. 1,25-dihydroxycholecalciferol is the metabolite responsible for the increase in calcium absorption. The vitamin D_3 that is not metabolised is stored in adipose and muscle tissue.

*Elimination:*vitamin D3 is primarily excreted in faeces; only a small amount is excreted in urine. The plasma half-life of vitamin D is in the order of several days.

5.3 Preclinical safety data

Calcium carbonate and cholecalciferol did not show mutagenic potential in vitro (Ames test).

A teratogenic effect has been observed in animal studies at very much higher doses than human therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Microcrystalline cellulose
Povidone
Crospovidone type A

Sodium laurilsulfate
Sodium croscarmellose
Magnesium stearate
DL-α-tocopherol
Partially hydrogenated soya bean oil
Sucrose
Bovine gelatin hydrolyzed
Corn starch
Silicon dioxide

Tablet Coat:
Light liquid paraffin
Talc
OPADRY OY-S-27203:
methylhydroxypropylcellulose
titanium dioxide (E171)
light liquid paraffin
sodium laurilsulfate
red iron oxide (E172)
black iron oxide (E172)
yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Opaque white high density polyethylene bottles with a polypropylene cap and induction sealed foil liner.

Bottles contain 20, 30, 60, 90 or 180 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Haleon Ireland Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/156/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th April 2009
Date of last renewal: 1st August 2013

10 DATE OF REVISION OF THE TEXT

April 2023