

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Per tablet:

Calcium carbonate: 750 mg equivalent to 300 mg of elemental calcium.

Colecalciferol: 200 I.U. equivalent to 5 µg vitamin D₃.

This product also contains sucrose (part of the vitamin D₃ concentrate: approximately 0.4 milligrams per tablet).

For full list of excipients see 6.1.

3 PHARMACEUTICAL FORM

Pale orange capsule-shaped film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an adjunct to specific therapy for osteoporosis and in situations requiring therapeutic supplementation of malnutrition e.g. in pregnancy and established vitamin D dependent osteomalacia.

The prevention and treatment of calcium deficiency/vitamin D deficiency especially in the housebound and institutionalised elderly subjects. Deficiency of the active moieties is indicated by raised levels of PTH, lowered 25-hydroxy vitamin D and raised alkaline phosphatase levels which are associated with increased bone loss.

4.2 Posology and method of administration

Oral.

Adults and Elderly and children above 12 years of age:

Two tablets to be taken twice a day, preferably two tablets each morning and two tablets each evening.

Children:

Not recommended for children under 12 years.

4.3 Contraindications

Absolute contra-indications are hypercalcaemia resulting for example from myeloma, bone metastases or other malignant bone disease, sarcoidosis, primary hyperparathyroidism and vitamin D overdosage. Severe renal failure. Hypersensitivity to any of the tablet ingredients.

Relative contra-indications are osteoporosis due to prolonged immobilisation, renal stones, severe hypercalciuria.

4.4 Special warnings and precautions for use

Patients with mild to moderate renal failure or mild hypercalciuria should be supervised carefully including periodic checks of plasma calcium levels and urinary calcium excretion.

In patients with a history of renal stones, urinary calcium excretion should be measured to exclude hypercalciuria.

With long-term treatment it is advisable to monitor serum and urinary calcium levels and kidney function, and reduce or stop treatment temporarily if urinary calcium exceeds 7.5 mmol/24 hours (300 mg/24 hours).

During concomitant treatment with other high-dose sources of vitamin D and/or medications affecting serum calcium levels or absorption, or nutrients containing calcium (see section 4.5), there is a risk of hypercalcaemia and milk-alkali syndrome (See section 4.9). In these patients, serum calcium levels and renal function should be monitored.

Caution is required in patients receiving treatment for cardiovascular disease (see Section 4.5 – thiazide diuretics and cardiac glycosides including digitalis).

Adcal-D3 Caplets should also be used with caution in other patients with increased risk of hypercalcaemia e.g. patients with sarcoidosis or those suffering from malignancies.

This product contains small quantities of sucrose.

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

Allowances should be made for calcium and vitamin D supplements from other sources.

Adcal-D3 Caplets should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of hypercalcaemia should be considered in patients taking thiazide diuretics since these drugs can reduce urinary calcium excretion. Hypercalcaemia must be avoided in digitalised patients.

Certain foods (e.g. those containing oxalic acid, phosphate or phytic acid) may reduce the absorption of calcium.

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

The effects of digitalis and other cardiac glycosides may be accentuated with the oral administration of calcium combined with Vitamin D. Strict medical supervision is needed and, if necessary, monitoring of ECG and calcium.

Calcium salts may reduce the absorption of thyroxine, bisphosphonates, sodium fluoride, quinolone or tetracycline antibiotics, zinc, strontium ranelate and iron. It is advisable to allow a minimum period of four hours before taking calcium.

Concomitant treatment with orlistat may reduce absorption of vitamin D.

4.6 Fertility, Pregnancy and lactation

During pregnancy and lactation, treatment with Adcal-D3 Caplets should always be under the direction of a physician. Requirements for calcium and vitamin D are increased during pregnancy and lactation, but, in deciding on the required supplementation, allowances should be made for availability of these agents from

other sources. If the patient requires administration of both Adcal-D3 Caplets and iron supplements, they should be taken at different times (see Section 4.5).

Overdoses of vitamin D have shown teratogenic effects in pregnant animals. However, there have been no studies on the use of this medicinal product in human pregnancy and lactation. In humans, long term hypercalcaemia can lead to physical and mental retardation, aortic stenosis and retinopathy in a new born child. Vitamin D and its metabolites pass into the breast milk.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Hypersensitivity reactions including pruritus, wheezing, urticaria, oropharyngeal swelling and angioedema have been reported in the post-marketing environment.

The use of calcium supplements has, rarely, given rise to mild gastro-intestinal disturbances, such as constipation, flatulence, nausea, gastric pain or diarrhoea. Following administration of vitamin D supplements occasional skin rash has been reported. Hypercalciuria, and in rare cases hypercalcaemia, have been seen with long term treatment at high dosages.

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

4.9 Overdose

The most serious consequence of acute or chronic overdose is hypercalcaemia due to vitamin D toxicity. Symptoms may include nausea, vomiting, polyuria, anorexia, weakness, apathy, thirst and constipation. Chronic overdoses can lead to vascular and organ calcification as a result of hypercalcaemia. Treatment should consist of stopping all intake of calcium and vitamin D and rehydration.

Milk-alkali syndrome may occur in patients who ingest large amounts of calcium.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Strong evidence that supplemental calcium and vitamin D₃ can reduce the incidence of hip and other non-vertebral fractures derives from an 18 month randomised placebo controlled study in 3270 healthy elderly women living in nursing homes or apartments for elderly people. A positive effect on bone mineral density was also observed.

In patients treated with 1200mg elemental calcium and 800IU vitamin D₃ daily, i.e. the same dose delivered by the twice daily administration of two Adcal-D3 Caplets, the number of hip fractures was 43% lower ($p=0.043$) and the total number of non vertebral fractures was 32% lower than among those who received placebo. Proximal femur bone mineral density after 18 months of treatment increased 2.7% in the calcium/vitamin D₃ group and decreased 4.6% in the placebo group ($p<0.001$). In the calcium/vitamin D₃ group, the mean serum PTH concentration decreased by 44% from baseline at 18 months and serum 25-hydroxy-vitamin D concentration had increased by 162% over baseline.

Analysis of the intention-to-treat results showed a decreased probability of both hip fractures ($p=0.004$) and other fractures ($p < 0.001$) in the calcium/vitamin D₃ treatment group. Analysis of the other two populations (active treatment and those treated and followed for 18 months) revealed comparable results to the intention-to-treat analysis. The odds ratio for hip fractures among women in the placebo group compared with those in the calcium/vitamin D₃ group was 1.7 (95% CI 1.0 to 2.8) and that for other nonvertebral fractures was 1.4 (95% CI 1.4 to 2.1). In the placebo group, there was a marked increase in the incidence of hip fractures over time whereas the incidence in the calcium/vitamin D₃ group was stable.

Thus treatment reduced the age-related risk of fracture at 18 months ($p = 0.007$ for hip fractures and $p = 0.009$ for all non-vertebral fractures). At 3 years follow-up, the decrease in fracture risk was maintained in the calcium/vitamin D₃ group.

5.2 Pharmacokinetic properties

The pharmacokinetic profiles of calcium and its salts are well known. Calcium carbonate is converted to calcium chloride by gastric acid. Calcium is absorbed to the

extent of about 15-25% from the gastro-intestinal tract while the remainder reverts to insoluble calcium carbonate and calcium stearate, and is excreted in the faeces.

The pharmacokinetics of vitamin D is also well known. Vitamin D is well absorbed from the gastro-intestinal tract in the presence of bile. It is hydroxylated in the liver to form 25-hydroxycholecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1, 25 dihydroxycholecalciferol (calcitriol). The metabolites circulate in the blood bound to a specific α - globin. Vitamin D and its metabolites are excreted mainly in the bile and faeces.

5.3 Preclinical safety data

Calcium carbonate and vitamin D are well known and widely used materials and have been used in clinical practice for many years. As such, toxicity is only likely to occur in chronic overdosage where hypercalcaemia could result.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Colloidal silicon dioxide
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Modified food starch
Sucrose
Sodium ascorbate cryst.
Medium chain triglycerides
Silicon dioxide
DL-alpha-tocopherol
Pregelatinized starch

Film-coat:

Hypromellose
Polydextrose
Acacia

Talc
Titanium dioxide
Iron oxide yellow
Iron oxide red

6.2 Incompatibilities

Not applicable, oral preparation.

6.3 Shelf life

18 months in HDPE bottle.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

HDPE bottle with polyethylene cap and silica gel dessicant: Pack sizes 112 or 224 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special conditions.

7 MARKETING AUTHORISATION HOLDER

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Saint Cloud Way
Maidenhead
Berkshire
SL6 8BN
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL21727/0105

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