For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

CCM TABLETS
Calcium Citrate Malate, Vitamin D₃ and Folic Acid Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

- Calcium Citrate Malate USP equivalent to Calcium 250 mg
- Cholecalciferol Concentrate (Powder Form) IP equivalent to Cholecalciferol (Vitamin D₃) 100 IU
- Folic Acid IP 50 mcg
- Excipients q.s.
- Colour: Titanium Dioxide IP

PHARMACEUTICAL FORM

Film coated tablets.

CLINICAL PARTICULARS

Therapeutic Indications

For the treatment of calcium and vitamin D deficiency state (pregnancy, lactation, growing children).

Posology and Method of Administration

The dose for children and adults may be adjusted according to the dietary intake of calcium, vitamin D and folic acid.

The duration of therapy depends on the response to therapy.

Additional calcium, vitamin D may be supplemented through diet or other sources to fulfill the requirements.

In case of Folic acid deficiency, additional supplementation will be required through diet or other sources.

Adults

2 tablets twice daily.

Children

2 tablets per day in one or two divided doses.

The ability of the child to take CCM tablets should be taken into account before prescribing it to children, particularly to young children.

Renal impairment
CCM should not be used in patients with severe renal impairment (see Contraindications & Special Warnings and Special Precautions for Use). Using in patients with renal failure is contraindicated (see Contraindications).

**Hepatic Impairment**

No dose adjustment is required.

**Contraindications**

CCM is contraindicated in:

- hypersensitivity to the active substances or to any of the excipients,
- hypercalcaemia, hypercalciuria,
- nephrocalcinosis, nephrolithiasis,
- disease and/or conditions resulting in hypercalcaemia and/or hypercalciuria (e.g. primary hyperparathyroidism, myeloma, bone metastases),
- hypervitaminosis D,
- severe renal impairment and renal failure (see Special Warnings and Special Precautions for Use).

**Special Warnings and Special Precautions for Use**

**Long term treatment**

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 Interactions with Other Medicaments and Other Forms of Interaction) and in patients with a high tendency to calculus formation. In case of hypercalcaemia or signs of impaired renal function the dose should be reduced or the treatment discontinued. Therapy should be reduced or preliminary interrupted, if urinary calcium level exceeds 7.5 mmol/24 h (300 mg/24 h).

**Sarcoidosis**

CCM 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.

**Immobilised patients with Osteoporosis**

CCM should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

**Renal impairment**

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. Patients with renal impairment are at potential risk of hyperphosphataemia, nephrolithiasis and nephrocalcinosis. 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 Contraindications).

**Other medicinal products containing calcium or vitamin D**

The content of vitamin D in CCM 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. Calcium and vitamin D intake from other sources (food, dietary supplements) should be estimated, before prescribing the product.

**Tetracyclines or quinolones**

Co-administration with tetracyclines or quinolones is usually not recommended, or must be done with precaution (see *Interaction with Other Medicaments and Other Forms of Interaction*).

**Interaction with Other Medicaments and Other Forms of Interaction**

*Phenytoin, barbiturates*

Concomitant use of phenytoin or barbiturates may reduce the effect of vitamin D₃ since the metabolism increases.

*Antiepileptics*

Folic acid has been reported to decrease serum concentrations of phenobarbital and phenytoin. Antiepileptics may produce folate deficiency states. Replacement therapy with folinic acid or folic acid may become necessary during antiepileptic therapy in order to prevent development of megaloblastic anaemia.

*Thiazide diuretics*

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.

*Corticosteroids*

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of CCM.

*Ion exchange resins, liquid paraffin*

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 should be recommended.

*Tetracyclines*

Calcium 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.

*Quinolone*

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.

*Penicillamine & Isoniazid*

Penicillamine (a chelating agent) and antituberculous drugs (such as isoniazid) may increase the requirements for folic acid.
Cardiac glycosides

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.

Bisphosphonate

If a bisphosphonate is used concomitantly, this preparation should be administered at least one hour before the intake of CCM since gastrointestinal absorption of may be reduced.

Sodium fluoride

Calcium may also reduce absorption of sodium fluoride and such preparations should be administered at least three hours before the intake of CCM.

Iron, zinc and strontium ranelate

Calcium salts may decrease the absorption of iron, zinc and strontium ranelate. Consequently, iron, zinc or strontium ranelate preparations should be taken at least two hours before or after calcium/cholecalciferol.

Oxalic acid, phytic acid

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.

Levothyroxine

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.

Folic acid antagonists

Folate deficiency states may be produced by folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim and sulfonamides.

Oral contraceptives

Serum concentration of folic acid may be decreased by use of oral contraceptives.

Alcohol

Alcohol may produce folate deficiency states.

Orlistat

Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins, e.g. vitamin D3.

Pregnancy and Lactation

Fertility

Normal endogenous levels of calcium and vitamin D are not expected to have any adverse effects on fertility.
**Pregnancy**

Calcium /cholecalciferol can be used during pregnancy, in case of a calcium and vitamin D deficiency. The daily intake should not exceed 1,500 mg of calcium and 600 I.U. of vitamin D.

Studies in animals have shown reproductive toxicity of high doses of vitamin D.

In pregnant women, overdoses of calcium and vitamin D should be avoided, as permanent hypercalcaemia has been related to adverse effects on developing foetus.

The physiological requirement of folic acid during pregnancy cannot be met with CCM alone. Additional folic acid should be supplemented through diet or other sources to fulfill the folic acid requirements during pregnancy and lactation.

**Lactation**

Calcium /cholecalciferol can be used during breast-feeding.

Calcium passes slightly into breast-milk, without having a negative effect on children.

Vitamin D and its metabolites also pass into breast-milk. This should be considered when giving additional vitamin D to the child.

Folic acid is excreted in breast milk.

**Effects on Ability to Drive and Use Machines**

There are no clinical data proving that the contents of CCM may have an influence on the ability to drive or use machines.

**Undesirable Effects**

**Clinical Trial Data**

There are no relevant data available

**Post Marketing Data**

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

- Very common \( \geq 1/10 \)
- Common \( \geq 1/100 \) to \( < 1/10 \)
- Uncommon \( \geq 1/1000 \) to \( < 1/100 \)
- Rare \( \geq 1/10000 \) to \( < 1/1000 \)
- Very rare \( < 1/10000 \)
- Not known (cannot be estimated from the available data).

*Immune system disorders*

*Not known:* hypersensitivity reactions (see Skin and subcutaneous tissue disorders; Respiratory, thoracic and mediastinal disorders), anaphylactic reaction.

*Metabolism and nutrition disorders*

*Uncommon:* hypercalcaemia, hypercalciuria.
Respiratory, thoracic and mediastinal disorders
Not known: laryngeal oedema.

Gastrointestinal disorders
Rare: nausea, diarrhea, abdominal pain, constipation, flatulence, abdominal distension.
Not known: vomiting.

Skin and subcutaneous tissue disorders
Rare: rash, pruritus, urticaria.
Not known: angioedema.

Overdose

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

The threshold for vitamin D intoxication is between 40,000 and 100,000 I.U./day for 1-2 months in persons with normal parathyroid function, for calcium in excess of 2.000 mg per day.

There are no reports of folic acid overdosage in the literature.

Treatment
In the case of intoxication, treatment should be stopped immediately and the fluid deficiency should be balanced. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued.

Rehydration and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should be given. Serum electrolytes, renal function and diuresis must be monitored. In severe cases ECG and CVP should be followed.

Further management should be as clinically indicated

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties
Nearly all (99%) of total body calcium is located in the skeleton. The remaining 1% is equally distributed between the teeth and soft tissues, with only 0.1% in the extracellular fluid (ECF). In the skeleton it constitutes 25% of the dry weight. Calcium in form of calcium phosphate which approximates hydroxyapatite \([\text{Ca}_{10}(\text{OH})_{2}(\text{PO}_4)_6]\) and embedded in collagen fibrils provide rigidity to the skeleton. Calcium ions play a role in many, if not most, metabolic processes. Calcium is essential, both during pregnancy and lactation, for proper formation of bones and teeth of the offspring, for secretion of breast-milk rich in calcium and to prevent osteoporosis in the mother.

Vitamin D is required to maintain normal blood levels of calcium and phosphate, which are in turn needed for the normal mineralization of bone, muscle contraction, nerve conduction, and general cellular function in all cells of the body. Vitamin D achieves this after its conversion to the active form 1,25-dihydroxyvitamin D \([1,25-(\text{OH})_2\text{D}]\), or calcitriol. This active form regulates
the transcription of a number of vitamin D-dependent genes which code for calcium-transporting proteins and bone matrix proteins. Vitamin D also modulates the transcription of cell cycle proteins, which decrease cell proliferation and increase cell differentiation of a number of specialized cells of the body (e.g. osteoclastic precursors, enterocytes, keratinocytes). This property may explain the actions of vitamin D in bone resorption, intestinal calcium transport, and skin.

Administration of calcium and vitamin D counteracts the increase of parathyroid hormone (PTH) which is caused by calcium deficiency and which cause increased bone resorption.

Folic acid is essential for erythropoiesis, maturation of red blood cells and biosynthesis of the DNA.

**Pharmacokinetic Properties**

**Calcium citrate malate**

Calcium is absorbed from small intestine in ionic form by both active and passive mechanisms. Overall, results from human and animal studies show that calcium from calcium citrate malate is more bioavailable (8–15%) than calcium from some other calcium sources. Citrate and malate anions chelated to calcium in calcium citrate malate are considered to enhance calcium absorption, possibly by forming relatively stable soluble complexes, such that precipitation of calcium by phosphate in the gut is not chemically favored and the likelihood of calcium absorption is improved. Active mechanism for calcium absorption depends on the action of the active form of vitamin D, 1,25-dihydroxycholecalciferol. Calcium that is unabsorbed from intestine is excreted in feces. Greater than 98% of calcium from glomerular filtrate is reabsorbed.

Approximately 40% of calcium in the plasma is bound to proteins, primarily albumin; about 50% of calcium in the plasma is diffusible ionic calcium and about 10% is diffusible, but it is complexed with anions such as phosphate and citrate.

**Cholecalciferol**

About 50-80% of the ingested vitamin D is absorbed in the small intestine. It is carried to the blood stream by lymphatics and it binds to alpha-globulin vitamin D in the blood. A large fraction of the circulating vitamin D is extracted by the hepatocytes and converted to 25-hydroxy vitamin D (25(OH)D) with the help of the enzyme, 25-hydroxylase. 25(OH)D is the major circulating form of vitamin D and it is actively converted to 1,25-dihydroxyvitamin D in the kidneys by the enzyme 125-hydroxyvitamin D1-alpha-hydroxylase. Deactivation of 1,25-dihydroxyvitamin D and 25(OH)D occurs by CYP24. Vitamin D and its metabolites are primarily excreted via the biliary root. The final degradation product of 1,25-dihydroxyvitamin D is calcitroic acid, which is excreted by the kidneys.

**Folic acid**

Folic acid is absorbed in the small intestine and transported to the liver. In the liver it is metabolized to polyglutamate forms and released into the circulation and to the bile. The principal folate in the plasma is 5-methyltetrahydrofolate in its monoglutamate form. About two-thirds of folate in plasma is protein bound. All tissue forms of folate are polyglutamates, while circulating forms are monoglutamates. Folate is excreted in the urine as folate cleavage products. Intact folate is reabsorbed into proximal convoluted tubule. Folate is excreted in bile and much of it is reabsorbed via the enterohepatic circulation.

**Clinical Studies**

A clinical study of institutionalised patients suffering from vitamin D deficiency indicated that a daily intake of 1000 mg calcium and 800 IU vitamin D for six months normalised the value of the 25-hydroxylated metabolite of vitamin D3 and reduced secondary hyperparathyroidism and alkaline phosphatases.

An 18 month double-blind, placebo controlled study including 3270 institutionalised women aged 84 (± 6 years) who received supplementation of vitamin D (800 IU/day) and calcium phosphate (corresponding to
1200 mg/day of elemental calcium), showed a significant decrease of PTH secretion. After 18 months, an "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). A follow-up study after 36 months showed 137 women with at least one hip fracture in the calcium-vitamin D group (n=1176) and 178 in the placebo group (n=1127) (p<0.02).

Preclinical Safety Data

At Vitamin D doses far higher than the human therapeutic range teratogenicity has been observed in animal studies.

PHARMACEUTICAL PARTICULARS

List of Excipients

Maize Starch, Methylparaben, Propylparaben, Polyvinylpyrrolidone K-30, Colloidal Silicon Dioxide (Degussa) and Magnesium Stearate.

Film-Coating:

Instacoat Universal (Code No. IC-U-3521)*

*Instacoat Universal (Code No. IC-U-3521) contains: Hydroxy propyl methyl cellulose, Polyethylene glycol, Talc, Titanium dioxide.

Incompatibilities

There are no relevant data available.

Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Store the container well closed at a temperature not exceeding 30°C. Protect from light and moisture. Keep out of reach of children.

Nature and Specification of Container

Bottles containing tablets in a carton.

Instructions for Use/Handling

There are no special requirements for use or handling of this product.

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  • Calcium +Cholecalciferol NCDS Version number 04 dated 24 July 2017
• EFSA. Calcium citrate malate as source for calcium for use in foods for particular nutritional uses and in foods for the general population (including food supplements). The EFSA Journal 2007;612:1-24.
• ICMR. Nutrient requirements and recommended dietary allowances for Indians. 2010. Hyderabad. ICMR.
• Schedule V, Drugs and Cosmetics Rules 1945.
• THERAGRAN STRESS Version number 03 dated 18 September 2018
• WHO. Vitamin and mineral requirements in human nutrition, 2nd ed. 2004.
• Vitamins and Minerals Checklist for Local Operating Companies (received from SERM).