SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CalciD-Denk

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances: calcium, colecalciferol

Each effervescent tablet contains 1,000 mg calcium (as calcium carbonate) and 22 µg colecalciferol (vitamin D_3, equivalent to 880 I.U.).

Excipients with known effect: Each effervescent tablet contains 396 mg lactose monohydrate, 3.7 mg sucrose, 94.5 mg sodium and soya oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Effervescent tablet
Round, white to off-white biplane effervescent tablets with bevelled edges on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As support for a specific osteoporosis treatment in patients with proven or high risk of simultaneous calcium and vitamin D deficiencies.

Compensation for simultaneous calcium and vitamin D deficiency in the elderly.

Calcium carbonate and colecalciferol are for use by adults.

4.2 Posology and method of administration

Posology
1 effervescent tablet once a day.

Paediatric population
Calcium carbonate and colecalciferol are not intended for use in children and adolescents.

Dosage in patients with hepatic impairment
No dose adjustment is required.

Dosage in patients with renal impairment
Calcium carbonate and colecalciferol are not permitted to be used in patients with severe renal impairment.

Method of administration
Oral ingestion after dissolving. The effervescent tablets are to be dissolved in a glass of water for immediate drinking.

Length of use
Treatment of the calcium deficiency and osteoporosis is to be applied for the long term. Treatment duration is based on the targeted therapeutic goal.

4.3 Contraindications

Calcium carbonate and colecalciferol are not permitted to be used in patients with:

- Hypersensitivity to the active substances, soy, peanuts, or any of the excipients listed in section 6.1.
- Illnesses or circumstances that can cause hypercalcaemia or hypercalciuria.
- Severe renal insufficiency.
- Kidney stones, nephrocalcinosis.
- Longer immobilization accompanied by hypercalciuria or hypercalcaemia.
- Hypervitaminosis D.

4.4 Special warnings and precautions for use

During long-term treatment the calcium level in the serum must be monitored and the renal function should be checked by measuring the serum creatinine. This monitoring is particularly important in older patients receiving concomitant treatment with cardiac glycosides or diuretics (see section 4.5) and in patients with a strong predisposition to the formation of stones or a positive family history of kidney stones containing calcium. In the event of hypercalcaemia or indications of impaired renal function, the dose must be reduced or the treatment must be discontinued.

Blood and urine calcium levels must be regularly monitored in patients who have been immobilised for a prolonged period of time.

Vitamin D should be used with caution in patients with renal impairment, and the calcium and phosphate levels should be checked. The risk of soft tissue calcification must be considered. Vitamin D in the form of colecalciferol is not metabolized normally in patients with severe renal impairment, and therefore other forms of vitamin D should be administered (see section 4.3).

Calcium carbonate and colecalciferol should be used with caution in 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 level in the serum and urine.

Calcium carbonate and colecalciferol should not be taken by people with pseudohypoparathyroidism (the vitamin D requirement can be reduced by the phase-wise normal vitamin D sensitivity with the risk of a long-lasting overdose). More easily controllable vitamin D derivatives are available for this.

During the first months of the calcium administration increased calcium excretion in the urine occurs that can further stone formation. This can be avoided by drinking ample liquids.

If other medicines containing vitamin D are prescribed, the vitamin D_3 dose (880 I.U.) in calcium carbonate and colecalciferol must be taken into consideration. The calcium and alkali absorption from other sources (food, dietary supplements, and other medicines) must be taken into consideration when calcium carbonate and colecalciferol is taken. High doses of calcium or vitamin D are only permitted to be taken under strict supervision by a physician. In such cases, frequent checks of the serum calcium

level and the calcium excretion in the urine are required. Taking high calcium doses concomitantly with absorbable alkaline substances (such as carbonates) can lead to milk-alkali syndrome (Burnett syndrome), i.e. hypercalcaemia, metabolic alkalosis, renal insufficiency and soft tissue calcification.

Calcium carbonate and colecalciferol can damage the teeth (caries).

Information regarding the use in certain groups of patients
Calcium carbonate is converted into soluble chloride in the stomach, making it bioavailable. In patients with achlorhydria the solubility can be impaired and the bioavailability can be reduced. Bioavailability is guaranteed, however, if these patients take the medicine with a meal.

In patients who are also taking antacids, it should be kept in mind that calcium carbonate also has acid-binding properties.

This medicine contains lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains sucrose.
Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains sodium.
This medicinal product contains 94.5 mg sodium per effervescent tablet, equivalent to 4.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Thiazide diuretics reduce the calcium excreted in the urine. In the event of concomitant use of thiazide diuretics, the serum calcium level must be regularly checked due to the increased risk of hypercalcaemia.

Calcium carbonate can impede the absorption of tetracycline preparations taken at the same time. For this reason, tetracycline preparations must be taken at least two hours before or four to six hours after the oral administration of calcium.

Hypercalcaemia can increase the toxicity of cardiac glycosides during the treatment with calcium and vitamin D. A medical check including EEC and measurement of the serum calcium level is therefore required.

In the event of concomitant use of bisphosphonates or sodium fluoride, these preparations should be taken at least three hours before calcium carbonate and colecalciferol effervescent tablets, because otherwise absorption in the gastrointestinal tract can be reduced.

The efficacy of levothyroxine can be impaired by the concomitant use of calcium due to reduced absorption of levothyroxine. Administration of calcium and levothyroxine should therefore be separated by at least four hours.

The absorption of quinolone antibiotics can be impaired if calcium is taken at the same time. Quinolone antibiotics should therefore be administered two hours before or six hours after the ingestion of calcium.

Systemic corticosteroids reduce the calcium absorption. Concomitant use can necessitate an increase in

the dose of calcium carbonate and colecalciferol.

Concomitant treatment with ion exchange resins such as cholestyramine, laxatives such as paraffin oil or orlistat can reduce the absorption of vitamin D in the gastrointestinal tract.

Rifampicin, phenytoin or barbiturates can weaken the effect of vitamin D3 because they increase its metabolism rate.

Calcium salts can impair the absorption of iron, zinc and strontium. Iron, zinc or strontium preparations should consequently be given two hours before or after a calcium preparation.

Oxalic acid (e.g. in spinach, sorrel and rhubarb) and phytic acid (in whole grain products) can inhibit calcium absorption due to the formation of insoluble compounds with calcium ions. The patient should not take any calcium preparations within two hours before or after eating foods with a high content of oxalic or phytic acid.

Other products that contain calcium or vitamin D: Additional doses of calcium and vitamin D can lead to a significant increase in the calcium level in the blood and cause harmful side effects. Such products are only permitted to be taken together with calcium carbonate and colecalciferol under the strict supervision of a physician.

The absorption and consequently also the efficacy of some cephalosporins and many other medicinal products (e.g., ketoconazole, estramustine) is reduced by the concomitant use of calcium carbonate and colecalciferol. As a rule, an interval of at least two hours should therefore be kept between taking calcium carbonate and colecalciferol and taking other preparations.

Bioavailability of calcium carbonate and colecalciferol can be reduced by antacids and renal elimination can be prolonged due to alkalization of the urine.

Calcium salts reduce the absorption of phosphate due to the formation of poorly soluble salts.

4.6 Fertility, pregnancy and lactation

Pregnancy
Calcium carbonate and colecalciferol should only be taken during pregnancy if strictly indicated and should be dosed only as long as is absolutely necessary to remedy the deficiency. Overdoses of vitamin D during pregnancy must be avoided because a long-term hypercalcaemia can lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child.

The reasonable daily dose (from food or supplements) for pregnant and nursing women is normally 1000 - 1300 mg calcium. During pregnancy the daily intake should not exceed 1500 mg.

Lactation
Calcium carbonate and colecalciferol should not be used during lactation due to the high dose of vitamin D. Vitamin D and its metabolic products are excreted in the milk.

Fertility
No data are available on the influence of calcium and vitamin D on fertility.

4.7 Effects on ability to drive and use machines

No data are available on the effects of this medicinal product on the ability to drive a vehicle. An

adverse effect is unlikely, however.

4.8 Undesirable effects

Organ system classes (MedDRA)	**Uncommon** (≥ 1/1,000, < 1/100)	**Rare** (≥ 1/10,000, < 1/1,000)	**Very rare** (< 1/10,000)	**Unknown** (cannot be assessed on the basis of the available data)
Immune system disorders			Hypersensitivity reactions	Hypersensitivity reactions such as angioedema or laryngeal oedema
Metabolic and nutritional disorders	Hypercalcaemia, hypercalciuria		Milk-alkali syndrome (normally only with overdose)	
Gastrointestinal disorders		Constipation, dyspepsia, flatulence, nausea, abdominal pain, diarrhoea		
Skin and subcutaneous tissue disorders			Pruritus, rash and urticaria	

In very rare cases, soya oil may cause allergic reactions.

Patients with renal impairment
There is a potential risk of hypophosphataemia, nephrolithiasis and nephrocalcinosis.

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 national reporting system.

4.9 Overdose

An overdose can lead to hypervitaminosis and hypercalcaemia. Symptoms of hypercalcaemia include anorexia, sensation of thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, psychological disorders, polydipsia, polyuria, bone pain, nephrocalcinosis, kidney stones and, in severe cases, cardiac arrhythmias. Extreme hypercalcaemia can result in coma and death. A persistently high calcium level can result in irreversible damage to the kidneys and soft tissue calcification.

Treatment of hypercalcaemia: The treatment with calcium and vitamin D must be discontinued. Treatment with thiazide diuretics and cardiac glycosides must likewise be discontinued. The stomach of patients with impaired consciousness must be emptied. Rehydration and, depending on the severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids. The serum electrolytes, renal function, and diuresis must be monitored. In severe cases, an ECG should be performed and the central venous pressure (CVP) should be monitored.

5. PHARMACOLOGIGAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium, combinations with vitamin D and/or other substances;
ATC code: A12AX01.

Calcium
Calcium ions are crucially important in the activation of biological systems. The threshold for excitable membranes depends on the extracellular Ca^{2+} concentration. Calcium ions are furthermore involved in the regulation of the permeability of cell membranes. A deficiency of Ca^{2+} ions in the plasma increases the neuromuscular excitability while an excess reduces it.
Oral calcium administration promotes the remineralisation of the skeleton in the event of a calcium deficiency.

Vitamin D
Colecalciferol (vitamin D_3) is formed in the skin under the influence of UV radiation and is converted to its biologically active form 1,25-dihydroxycholecalciferol in two hydroxylation steps, first in the liver (position 25) and then in the kidney tissue (position 1). Together with parathormone and calcitonin, 1,25-dihydroxycholecalciferol is fundamentally involved in regulating the calcium and phosphate balance. In the event of a vitamin D deficiency, the calcification of the skeleton is absent (rachitis) or softening of the bones (osteomalacia) occurs.

After production, physiological regulation and mode of action, so-called vitamin D_3 is seen as a precursor of a steroid hormone. In addition to the physiological production in the skin, colecalciferol can be supplied with the food or as pharmacon. Because the latter way bypasses the physiological product inhibition of cutaneous vitamin D synthesis, overdoses and intoxications are possible. Ergocalciferol (vitamin D_2) is formed in plants. It is metabolically activated like colecalciferol in humans. It exercises the same effects in terms of quality and quantity.

5.2 Pharmacokinetic properties

Calcium
Absorption
Calcium absorption is subject to hormonal regulation. The absorption rate decreases as the dose and age increase and increases under hypocalcaemic conditions. When 500 mg calcium citrate are supplied, roughly 30 - 40% is absorbed. The administration of higher doses leads only to a slight increase in the absorbed quantity. The normal daily calcium supply with the food is roughly 1,000 mg.

Distribution and biotransformation
99% of the calcium in the body is concentrated in the hard structures of the bones and teeth. The remaining 1% is located in the intra- and extracellular fluids. Around 50% of the total calcium in the blood is present in the physiologically active ionised form, with roughly 10% of the calcium complex binding to citrate, phosphate or other anions and the remaining 40% to proteins, primarily albumin.

Elimination
Depending on the serum calcium level, calcium is excreted through the kidneys. In people with healthy kidneys, 98% of the filtered calcium is tubularly reabsorbed.

Vitamin D
Absorption

In alimentary doses, vitamin D from the food is almost completely absorbed in the intestines together with the dietary lipids and bile acids. Higher doses are absorbed at a rate of roughly 2/3. In the skin, the vitamin D is synthesized from 7-dehydrocholesterol under the influence of UV light.

Distribution and biotransformation
With the help of a specific transport protein, the vitamin D reaches the liver where it is metabolised to 25-hydroxycholecalciferol by microsomal hydroxylation.

Vitamin D is stored in adipose tissue and therefore has a long biological half-life. After high vitamin D doses, the 25-hydroxy vitamin-D concentrations in the serum can be elevated for months. Hypercalcaemia caused by an overdose can be present for weeks (see section 4.9).

Elimination
Vitamin D and its metabolites are excreted in the bile and faeces.

5.3 Preclinical safety data

In animal studies, teratogenicity was observed in doses that were far higher than the therapeutic range for humans. No further information related to safety is available other than the information provided in other sections of this SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Alpha-tocopherol, hydrogenated soya oil, gelatin, sucrose, maize starch, citric acid, sodium hydrogen carbonate, lactose monohydrate, povidone, saccharin sodium, sodium cyclamate, macrogol 6000, simeticone, methyl cellulose, orange juice flavour.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original carton in a dry place below 25°C.
Keep the tube tightly closed to protect content from moisture.

6.5 Nature and contents of container

Polypropylene tubs with desiccant stoppers made of polyethylene.

20 effervescent tablets per tube.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Denk Pharma GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBER IN GERMANY

63838.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

27.04.2006

10. DATE OF REVISION OF THE TEXT

09/2019

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription