SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cholecalciferol mibe 500 IE, tabletten
Cholecalciferol mibe 1000 IE, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cholecalciferol mibe 500 IE, tabletten:
Each tablet contains 12.5 microgram of cholecalciferol (equivalent to 500 IU vitamin D_3), as cholecalciferol concentrate, powder form.

Cholecalciferol mibe 1000 IE, tabletten:
Each tablet contains 25 microgram of cholecalciferol (equivalent to 1000 IU vitamin D_3), as cholecalciferol concentrate, powder form.

Excipients with known effect:
One tablet Cholecalciferol mibe 500 IE, tabletten contains 34.47 mg lactose monohydrate and 0.87 mg sucrose.
One tablet Cholecalciferol mibe 1000 IE, tabletten contains 68.94 mg lactose monohydrate and 1.73 mg sucrose.
Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten contains less than 1 mmol sodium (23 mg) per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Cholecalciferol mibe 500 IE, tabletten are round, biconvex, white to yellowish tablets.

Cholecalciferol mibe 1000 IE, tabletten are oblong, biconvex, white to yellowish tablets with score line. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Prophylaxis of rickets and osteomalacia in children, adolescents and adults
- Prophylaxis of vitamin D deficiency in children, adolescents and adults with an identified risk
- As an adjunct to specific therapy of osteoporosis in adults

4.2 Posology and method of administration

Posology

Prophylaxis of rickets and osteomalacia in children, adolescents and adults

1 tablet Cholecalciferol mibe 500 IE, tabletten or ½ tablet Cholecalciferol mibe 1000 IE, tabletten daily (equivalent to 0.0125 mg or 500 IU vitamin D_3) (see section 4.4).

The dosage should be established by the treating physician. Generally, for the prophylaxis of rickets in preterm newborn infants,

- with a birth weight > 1500 g: 1 tablet Cholecalciferol mibe 500 IE, tabletten or ½ tablet Cholecalciferol mibe 1000 IE, tabletten daily (equivalent to 0.0125 mg or 500 IU vitamin D_3)
- with a birth weight < 1500 g (700 – 1500 g): 2 tablets Cholecalciferol mibe 500 IE, tabletten or 1 tablet Cholecalciferol mibe 1000 IE, tabletten daily (equivalent to 0.025 mg or 1000 IU vitamin D_3)

are recommended (see section 4.4).

Prophylaxis of vitamin D deficiency in children, adolescents and adults with an identified risk

Infants (0 - 12 months):
1 tablet Cholecalciferol mibe 500 IE, tabletten or ½ tablet Cholecalciferol mibe 1000 IE, tabletten daily (equivalent to 0.0125 mg or 500 IU vitamin D_3) (see section 4.4).

Children, adolescents and adults:
1 - 2 tablets Cholecalciferol mibe 500 IE, tabletten or ½ - 1 tablet Cholecalciferol mibe 1000 IE, tabletten daily (equivalent to 0.0125 – 0.025 mg or 500 - 1000 IU vitamin D_3) (see section 4.4).

As adjunct to specific therapy for osteoporosis in adults

2 tablets Cholecalciferol mibe 500 IE, tabletten or 1 tablet Cholecalciferol mibe 1000 IE, tabletten daily (equivalent to 0.025 mg or 1000 IU vitamin D_3) (see section 4.4).

During long-term treatment with Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten at daily doses above 500 IU, serum and urinary calcium levels should be monitored regularly and renal function checked via serum creatinine determination. If necessary, a dose adjustment should be made on the basis of serum calcium levels (see section 4.4).

Alternatively, national posology recommendations in prevention and treatment of vitamin D deficiency can be followed

Method of administration

Infants and toddlers

Rickets prophylaxis in infants**:**
Infants are given Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten from their second week of life up until the end of their first year of life. In their second year of life, further doses of Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten are to be recommended, especially during the winter months.

Dissolve the tablet on a teaspoon with water or milk and administer the dissolved tablet directly into the child’s mouth, preferably during a meal. The disintegration takes 1-2 minutes. For accelerating the process of disintegration, spoon should be moved slightly.

Adding dissolved tablets to a baby’s bottle feed or soft mashed food is not recommended, as complete administration cannot be guaranteed. Nevertheless, if the tablets are to be administered with food, it should first be cooked and then allowed to cool before the tablets are added.

When using vitamin-enriched food, the amount of vitamin D contained therein should be taken into account.

Adults

The tablets are to be taken with sufficient water.

The duration of treatment depends on the progression of the disease.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypercalcaemia
- Hypercalciuria
- Hypervitaminosis D
- Renal calculi

4.4 Special warnings and precautions for use

When prescribing other medicinal products containing vitamin D, the vitamin D dose of Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten should be taken into account. Adjuvant vitamin D or calcium should only be prescribed under medical supervision. In such cases, serum and urinary calcium levels must be monitored.

In patients with renal insufficiency treated with Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten, the effect on the calcium and phosphate balance should be monitored.

Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten should not be taken, if patients are susceptible to the formation of kidney stones containing calcium.

Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten should be used only with particular caution in patients with impaired renal calcium and phosphate excretion, when treating with benzothiadiazine derivatives and in immobilised patients (risk of hypercalcaemia, hypercalciuria). In these patients, the plasma and urinary calcium levels should be monitored.

Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten should be used only with caution in patients suffering from sarcoidosis, as there is a risk of increased conversion of vitamin D into its active metabolites. In these patients, the plasma and urinary calcium levels should be monitored.

Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten should not be taken if pseudohypoparathyroidism is present (the need for vitamin D may be reduced by the sometimes normal sensitivity to vitamin D, with a risk of long-term overdose). In such cases, more manageable vitamin D derivatives are available.

Infants and toddlers
Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten should be used with particular caution in infants and toddlers, as these may not be able to swallow the tablets and might choke. Instead, it is advisable to dissolve the tablets as stated (see section 4.2) or to use drops.

Daily doses above 500 IU
During long-term treatment with Cholecalciferol mibe, tabletten, serum and urinary calcium levels should be monitored and renal function checked via serum creatinine determination. Such monitoring is particularly important in elderly patients and during concomitant treatment with cardiac glycosides or diuretics. This also applies to patients who are particularly susceptible to the formation of kidney stones that contain calcium.

In the event of hypercalcaemia or signs of reduced renal function, the dose must be reduced or the treatment discontinued. If hypercalciuria occurs (more than 7.5 mmol equivalent to 300 mg calcium/24 hours), the dose is to be reduced or treatment discontinued.

Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten contains sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten contains lactose monohydrate
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Phenytoin or barbiturates
The plasma concentration of 25-OH D may be reduced and metabolism to inactive metabolites increased.

Glucocorticoids
Due to an increase in the metabolism of vitamin D, the effect of vitamin D may be impaired.

Rifampicin and isoniazid
The metabolism of vitamin D can be increased and its efficacy reduced.

Ion exchangers, laxatives, orlistat
The simultaneous treatment with ion exchangers such as cholestyramine, laxatives such as liquid paraffin or orlistat can reduce the gastrointestinal absorption of vitamin D.

Actinomycin and imidazole
May reduce the conversion of the vitamin D metabolites and therefore reduce the effectiveness.

Vitamin D metabolites or analogues (e.g. calcitriol)
Combination with Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten is recommended only in exceptional cases. Plasma calcium levels should be monitored.

Thiazide diuretics
Thiazide diuretics can lead to hypercalcaemia due to the reduction in renal calcium excretion. Plasma and urinary calcium levels should therefore be monitored during long-term therapy.

Digitalis (cardiac glycosides)
Oral administration of vitamin D can potentiate the efficacy and toxicity of digitalis as a result of an increase in calcium levels (risk of cardiac arrhythmias). Patients should be monitored with regard to ECG, calcium levels in the plasma and urine, as well as digoxin or digitoxin plasma levels, if applicable.

4.6 Fertility, pregnancy and lactation

Pregnancy

Daily intake up to 500 IU/d
In this dose range, there are no known risks to date.
Long-term overdoses of vitamin D must be avoided during pregnancy, as a resulting hypercalcaemia may lead to retardation of physical and mental development, supravalvular aortic stenosis and retinopathy in the child.

Daily intake more than 500 IU/d
During pregnancy, Cholecalciferol mibe 500 IE, tabletten / 1000 IE, tabletten should be taken only when strictly indicated and dosed only as it is absolutely necessary to correct the vitamin D deficiency. Overdoses of vitamin D must be avoided during pregnancy, as prolonged hypercalcaemia may lead to retardation of physical and mental development, supravalvular aortic stenosis and retinopathy in the child.

Breast-feeding

Vitamin D and its metabolites are excreted in human milk. There have been no observed cases of overdose produced in this way among infants. This should, however, be borne in mind when administering additional vitamin D to the child.

Fertility
No effects have been observed in reproductive fertility studies with cholecalciferol. The potential benefit/risk ratio for humans is unknown.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The frequencies of undesirable effects are not known, as no major clinical studies allowing any estimation of frequencies have been conducted.

Immune system disorders
Hypersensitivity reactions such as angioneurotic oedema or laryngeal oedema

Metabolism and nutrition disorders
Hypercalcaemia and hypercalciuria

Gastrointestinal disorders
Gastrointestinal complaints such as constipation, flatulence, nausea, abdominal pain or diarrhoea

Skin and subcutaneous tissue disorders
Pruritus, skin rash or urticaria

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:

Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

4.9 Overdose

Symptoms of an overdose
Acute and chronic overdose with vitamin D_3 can lead to hypercalcaemia, which may persist and possibly be life-threatening. The symptoms are uncharacteristic and may include cardiac arrhythmias, thirst, dehydration, adynamia and impaired consciousness. Furthermore, a chronic overdose may lead to calcium deposits in blood vessels and tissues.

In addition to a rise in serum and urinary phosphorus levels, an overdose can also lead to hypercalcaemia syndrome, which subsequently leads to calcium deposits within tissues and especially the kidneys (nephrolithiasis, nephrocalcinosis), as well as the blood vessels.

The symptoms of intoxication are not very characteristic, manifesting as nausea, vomiting, initial frequent diarrhoea progressing to constipation, anorexia, lassitude, headache, myalgia, arthralgia, muscle weakness and persistent drowsiness, arrhythmia, azotaemia, polydipsia and polyuria, and - at the preterminal stage - exsiccosis. Typical biochemical findings are hypercalcaemia, hypercalciuria and elevated serum levels for 25-hydroxycalciferol.

Therapeutic measures in the event of an overdose

Symptoms of a chronic overdose with vitamin D may necessitate forced diuresis as well as the administration of glucocorticoids and calcitonin.

In the event of an overdose, measures are required for the treatment of often chronic and potentially life-threatening hypercalcaemia.

As a primary measure, the vitamin D product should be discontinued; normalisation of hypercalcaemia as a result of vitamin D intoxication takes several weeks.

Depending on the extent of hypercalcaemia, a low-calcium or calcium-free diet, copious hydration, forced diuresis by means of furosemide and the administration of glucocorticoids and calcitonin can be used.

If renal function is adequate, infusions of isotonic NaCl solution (3-6 l in 24 hours) – with adjuvant furosemide and, in some cases, 15 mg/kg BW/hour sodium edetate, administered under continuous calcium and ECG monitoring – have a highly reliable calcium-reducing effect. However, haemodialysis therapy (with a calcium-free dialysate) is indicated for oligoanuria.

There is no known specific antidote.

It is recommended that patients on long-term treatment with higher vitamin D doses be informed about the symptoms of a possible overdose (nausea, vomiting, initial frequent diarrhoea progressing to constipation, anorexia, lassitude, headache, myalgia, arthralgia, muscle weakness, drowsiness, azotaemia, polydipsia and polyuria).

5. PHARMACOLOGICAL PROPERTIES

There are different recommendations available with regard to daily intake of vitamin D. The reference values for vitamin D valid in Germany, Austria and Switzerland (2013) are set for adults to 20 µg, equivalent to 800 IU per day. The Dutch Health Council (2012) and the Institute of Medicine (2011) recommend for the Netherlands 10 µg – 15 µg, equivalent to 400 IU – 600 IU per day for adults, and 20 µg for elderly > 70 years, equivalent to 800 IU per day. Healthy adults can cover their requirements via endogenous synthesis when sunlight exposure is adequate. Intake via food is only of secondary significance but may be of importance under certain critical conditions (climate, lifestyle).

Fish liver oil and fish are particularly rich in vitamin D, whilst low quantities are found in meat, egg yolk, milk, dairy products and avocado.

Signs of deficiency can appear, for instance, in immature preterm newborn infants, infants exclusively breast-fed for more than six months without calcium supplements, or children on a strict vegetarian diet. Causes for rarely occurring vitamin D deficiency in adults may be inadequate dietary intake, insufficient UV exposure, malabsorption and poor digestion, cirrhosis of the liver and renal insufficiency.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vitamin D and analogues, cholecalciferol
ATC code: A11CC05

Cholecalciferol (vitamin D_3) is synthesized in the skin from 7-dehydrocholesterol upon exposure to UV rays and is converted to its biologically active form (1,25 dihydroxycholecalciferol) in two hydroxylation stages - firstly within the liver (position 25) and then in kidney tissue (position 1). Together with parathormone and calcitonin, 1,25 dihydroxycholecalciferol plays an essential role in regulating the calcium and phosphate balance. In its biologically active form, vitamin D_3 stimulates intestinal calcium absorption, the incorporation of calcium into osteoid and calcium release from bone

tissue. In cases of vitamin D deficiency, skeletal calcification is absent (rickets) or bone decalcification occurs (osteomalacia).

Calcium and/or vitamin D deficiency induce reversible, increased secretion of parathormone. This secondary hyperparathyroidism causes increased bone turnover, which can lead to bone brittleness and fractures.

In terms of its production, physiological regulation and mechanism of action, so-called vitamin D_3 can be regarded as a precursor to a steroidal hormone.

In addition to its physiological production in the skin, cholecalciferol can be supplemented by food or as a medicinal product. Cases of overdose and intoxication are possible via the latter route, as physiological product inhibition of cutaneous vitamin D synthesis is circumvented.

Ergocalciferol (vitamin D_2) is produced in plants. In humans, it is metabolically activated like cholecalciferol. Ergocalciferol exerts the same effects, both qualitatively and quantitatively.

5.2 Pharmacokinetic properties

Absorption
At dietary doses, vitamin D is almost completely absorbed from food, together with nutritional lipids and bile acids. Higher doses are absorbed at an absorption rate of around two-thirds.

Distribution and biotransformation
Cholecalciferol and its metabolites circulate in the blood bound to proteins. In the liver, it is metabolised by a microsomal hydroxylase to 25-hydroxycholecalciferol. It is then converted in the kidneys to 1,25-dihydroxycholecalciferol.

Vitamin D, which is not metabolised, is stored in muscle and adipose tissue and therefore has a long biological half-life. After high vitamin D doses, 25-hydroxyvitamin D concentrations in serum may be elevated for months. Hypercalcaemia induced by an overdose may persist for weeks (see section 4.9).

Elimination
Excretion of vitamin D and its metabolites takes place via the biliary/faecal route.

5.3 Preclinical safety data

Apart from those mentioned in sections 4.6 and 4.9 of the Summary of Product Characteristics, there are no further specific toxicological hazards for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Maize starch
Modified maize starch
Sodium starch glycolate (type A) (Ph.Eur.)
Sucrose
Silica, colloidal anhydrous
Magnesium stearate (Ph.Eur.)
Sodium ascorbate
Medium-chain triglycerides
All-rac-alpha-tocopherol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Cholecalciferol mibe 500 IE, tabletten: 30 months.
Cholecalciferol mibe 1000 IE, tabletten: 3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Blister packs (PVC/PE/PVdC aluminium blister packs).
Cholecalciferol mibe 500 IE, tabletten: packs containing 20, 50, 100 and 200 tablets.
Cholecalciferol mibe 1000 IE, tabletten: packs containing 20, 30, 50, 100 and 200 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

mibe GmbH Arzneimittel
Münchener Straße 15
06796 Brehna
Germany

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8. MARKETING AUTHORISATION NUMBERS

Cholecalciferol mibe 500 IE, tabletten	RVG 113281
Cholecalciferol mibe 1000 IE, tabletten	RVG 113282

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 oktober 2013

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 2 en 4.2: 17 januari 2020

11. GENERAL CLASSIFICATION FOR SUPPLY

Prescription only