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

<trade name 500 IU>:
Each tablet contains 12.5 micrograms of cholecalciferol (equivalent to 500 IU vitamin D_3), as cholecalciferol concentrate, powder form.

<trade name 1000 IU>:
Each tablet contains 25 micrograms of cholecalciferol (equivalent to 1000 IU vitamin D_3), as cholecalciferol concentrate, powder form.

Excipients with known effect:
One tablet <trade name> 500 IU contains 32.75 mg lactose and 0.87 mg sucrose.
One tablet <trade name> 1000 IU contains 65.49 mg lactose and 1.73 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

<trade name> 500 IU are white to yellowish, round, slightly biconvex tablets of about 5 mm.

<trade name> 1000 IU are white to yellowish, oblong, biconvex tablets with a score line on both sides and a dimension of about 10 mm x 2.8 mm.
The tablet can be divided into equal halves.

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 for osteoporosis in adults

4.2 Posology and method of administration

Posology

Prophylaxis of rickets and osteomalacia in children, adolescents and adults
1 tablet <trade name> 500 IU or ½ tablet <trade name> 1000 IU 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 <trade name> 500 IU or ½ tablet <trade name> 1000 IU daily (equivalent to 0.0125 mg or 500 IU vitamin D_3)

- with a birth weight < 1500 g (700 - 1500 g): 2 tablets <trade name> 500 IU or 1 tablet <trade name> 1000 IU 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 <trade name> 500 IU or ½ tablet <trade name> 1000 IU daily (equivalent to 0.0125 mg or 500 IU vitamin D_3) (see section 4.4).

Children, adolescents and adults:
1 - 2 tablets <trade name> 500 IU or ½ - 1 tablet <trade name> 1000 IU 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 <trade name> 500 IU or 1 tablet <trade name> 1000 IU daily (equivalent to 0.025 mg or 1000 IU vitamin D_3) (see section 4.4).

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

Special populations

Patients with hepatic impairment
No dose adjustment is required.

Patients with renal impairment
No dosage adjustment is necessary in patients with an eGFR > 30 ml/min without hyperparathyroidism and hyperphosphatemia (see section 4.4).
<trade name> 500 IU / 1000 IU must not be used in patients with severe renal impairment (see section 4.3).

Method of administration

Infants and toddlers
Rickets prophylaxis in infants:
Infants are given <trade name> 500 IU / 1000 IU 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 <trade name> 500 IU / 1000 IU 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, preferably during a meal.

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
- Hypercalcemia
- Hypercalciuria
- Hypervitaminosis D
- Nephrocalcinosis
- Nephrolithiasis (Renal calculi)
- Severe renal impairment

4.4 Special warnings and precautions for use

Other vitamin D containing products
Before starting the vitamin D therapy, the patient's status, should be carefully evaluated by the doctor and artificially added vitamin D content of certain food types or other medicinal products containing Vitamin D must be taken into consideration. Combination of <trade name> 500 IU / 1000 IU with metabolites or analogues of vitamin D (e.g. calcitriol) have to be avoided. Additional vitamin D or calcium should only be administered under medical supervision to prevent hypercalcemia. In such cases, serum and urinary calcium levels must be monitored.
Combination with calcium supplements should take into account all sources of calcium and not exceed e.g. 1000 mg/day.

Renal impairment
In patients with mild to moderate renal insufficiency treated with <trade name> 500 IU / 1000 IU, the effect on the calcium and phosphate balance should be monitored. In patients with severe renal insufficiency, cholecalciferol may not be metabolized and <trade name> 500 IU / 1000 IU is contraindicated (see section 4.3).

Pseudohypoparathyroidism
<trade name> 500 IU / 1000 IU should not be taken if pseudohypoparathyroidism is present (The vitamin D requirement may be reduced by intermittent normal vitamin D sensitivity, with the risk of long-term overdose). In such cases, more manageable vitamin D derivatives are available.

Kidney stones
<trade name> 500 IU / 1000 IU should not be taken by individuals who are particularly susceptible to the formation of kidney stones that contain calcium.

Impaired calcium and phosphate excretion, during treatment with benzothiadiazine derivatives and immobilised patients
<trade name> 500 IU / 1000 IU should be used with particular caution in patients with impaired renal calcium and phosphate excretion, during treatment with benzothiadiazine derivatives and in immobilised patients (risk of hypercalcemia, hypercalciuria). In these patients, plasma and urinary calcium levels should be monitored. The risk of soft tissue calcification should be taken into account.

Sarcoidosis
<trade name> 500 IU / 1000 IU 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.

Monitoring of calcium levels
During long-term treatment with <trade name> 500 IU / 1000 IU, serum and urinary calcium levels should be monitored regularly and renal function checked via measurement of serum creatinine. If necessary, a dose adjustment should be made on the basis of serum calcium levels (see section 4.5).

During treatment with an equivalent daily dose exceeding 1 000 IU vitamin D the serum and renal calcium levels must 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 (see section 4.5). In the event of hypercalcemia, treatment has to be discontinued. If there are signs of reduced renal function, the dose must be reduced or the treatment

discontinued. When urinary calcium levels exceed 7.5 mmol/24 hours (300 mg/24 hours), treatment has to be discontinued (see section 4.3).

In patients with idiopathic infantile hypercalcemia (e.g. CYP24A1 mutation), the risk of hypercalcemia and secondary effects (e.g. hypercalciuria, nephrocalcinosis, nephrolithiasis) is increased due to accumulation of active vitamin D. Idiopathic infantile hypercalcemia may be asymptomatic and undiagnosed at the beginning of vitamin D therapy and may be unmasked and become clinically apparent after vitamin D supplementation.

Infants and toddlers
<trade name> 500 IU / 1000 IU 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.

<trade name> 500 IU / 1000 IU contains sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

<trade name> 500 IU / 1000 IU contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

<trade name> 500 IU / 1000 IU contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Medicinal products/drug substances that diminish the vitamin D effect

Anticonvulsants and antiepileptics
Concomitant use of anticonvulsants such as phenobarbital, hydantoin derivatives such as phenytoin, and other barbiturates or primidone, and possibly other drugs that induce hepatic enzymes may reduce the effect of vitamin D_3 by metabolic inactivation i.e. activation of the microsomal enzyme system.

Rifampicin
Rifampicin may reduce the effectiveness of cholecalciferol due to hepatic enzyme induction.

Isoniazid
Isoniazid may reduce the effectiveness of cholecalciferol due to inhibition of the metabolic activation of cholecalciferol.

Ion exchangers, laxatives, orlistat
Drugs leading to fat malabsorption, e.g. orlistat, laxatives (liquid paraffin, mineral oil) or ion exchange resins (cholestyramin or colestipol) can reduce the gastrointestinal absorption of vitamin D.

Actinomycin and imidazoles
The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D_3 activity by inhibiting the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol by the kidney enzyme, 25-hydroxyvitamin D-1-hydrolase.

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

Medicinal products/drug substances that increase the effect/side effects of vitamin D

Thiazide diuretics, Hydrochlorothiazide

Simultaneous administration of benzothiadiazine derivatives (thiazide diuretics) increase the risk of hypercalcemia due to the reduction in renal calcium excretion. Plasma and urinary calcium levels should therefore be monitored.

Medicinal products/drug substances whose risk of side effects may be increased by vitamin D

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 plasma and urine, as well as digoxin or digitoxin plasma levels, if applicable.

Calcitonin, Gallium nitrate, Bisphosphonates, Plicamycin
Concomitant use of calcitonin, gallium nitrate, bisphosphonates, or plicamycin with vitamin D may antagonise the effect of these products.

Magnesium containing products
Products containing magnesium (like antacids) may not be taken during vitamin D treatment because of the risk of hypermagnesemia.

Phosphor containing products
Products containing phosphor used in large doses, given concomitantly may increase the risk of hyperphosphatemia.

Aluminium containing products
Vitamin D may increase intestinal absorption of aluminium and hence increase aluminium serum levels. Long-term or excessive use of aluminium containing antacids should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of vitamin D in pregnant women. Vitamin D deficiency is harmful for mother and child. High doses of vitamin D have been shown to have teratogenic effects in animal experiments (see section 5.3).

Overdose of vitamin D must be avoided during pregnancy, as prolonged hypercalcemia may lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child.

Where there is a vitamin D deficiency the recommended dose is dependent on national guidelines, however, the maximum recommended dose during pregnancy is 4 000 IU/day vitamin D_3. For treatment during pregnancy at higher doses, <trade name> 1000 IU is not recommended during pregnancy.

Breast-feeding
Vitamin D_3 and its metabolites are excreted in breast milk. No adverse events have been observed in infants. <trade name> 500 IU / 1000 IU can be used at recommended doses during lactation in case of a vitamin D deficiency. This should be considered when giving additional vitamin D to the child.

Fertility
Normal endogenous levels of vitamin D are not expected to have any adverse effects on fertility. The impact of high doses of vitamin D on fertility is unknown.

4.7 Effects on ability to drive and use machines

<trade name> 500 IU / 1000 IU has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are listed below, by system organ class and frequencies.

MedDRA-system organ class database	**Frequency of undesirable effects**		
	Uncommon (≥1/1 000, <1/100)	**Rare** (≥1/10 000, <1/1 000)	**Not known** (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity reactions such as angioneurotic oedema or laryngeal oedema
Metabolism and nutrition disorders	Hypercalcemia and hypercalciuria		
Gastrointestinal disorders			Constipation, flatulence, nausea, abdominal pain, diarrhoea
Skin and subcutaneous tissue disorders		Pruritus, rash and 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:

<[to be completed nationally]>

4.9 Overdose

Symptoms of an overdose
Acute and chronic overdose with vitamin D_3 can lead to hypercalcemia, which may persist and possibly be life-threatening.
The symptoms of intoxication are not very characteristic, manifesting as thirst, dehydration, nausea, vomiting, initial frequent diarrhoea progressing to constipation, anorexia, lassitude, headache, myalgia, arthralgia, muscle weakness and persistent drowsiness, impaired consciousness, arrhythmia, azotaemia, polydipsia and polyuria, and (at the preterminal stage) exsiccosis.

Daily doses up to 500 IU/d
Chronic overdose with vitamin D can lead to hypercalcemia and hypercalciuria. If requirements are considerably exceeded over prolonged periods, calcification of the parenchymatous organs may occur.

Daily doses above 500 IU/d
Ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) have only a relatively narrow therapeutic margin. In adults with normal parathyroid function, the threshold for vitamin D intoxication is between 40 000 and 100 000 IU per day over 1 to 2 months. However, neonates and infants may experience sensitive reactions at much lower concentrations. Vitamin D supplementation is therefore not recommended without medical supervision.

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

Therapeutic measures in the event of an overdose

Daily doses up to 500 IU/d
Symptoms of a chronic overdose with vitamin D may necessitate forced diuresis as well as the administration of glucocorticoids and calcitonin.

Daily doses above 500 IU/d

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

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

Depending on the extent of hypercalcemia, 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 micrograms, equivalent to 800 IU per day. The Dutch Health Council (2012) and the Institute of Medicine (2011) recommend for the Netherlands 10 - 15 micrograms, equivalent to 400 IU - 600 IU per day for adults, and 20 micrograms 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. Hypercalcemia 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

Effects in non-clinical repeat-dose toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating such toxicity is only likely to occur in chronic overdosage where hypercalcemia could result.

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

Cholecalciferol has no potential mutagenic activity (negative in Ames-test) and no carcinogenic activity.

There is further no information of relevance to the safety assessment in addition to what is stated in other parts of the SPC (see section 4.6 and 4.9).

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

<trade name> 500 IU tablets: 30 months
<trade name> 1000 IU tablets: 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).
<trade name> 500 IU tablets: packs containing 20, 50, 100 and 200 tablets.
<trade name> 1000 IU tablets: 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
Duitsland

Tel.: 034954/247-0
Fax: 034954/247-100

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Datum van eerste verlening van de vergunning: 1 oktober 2013

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 2, 3, 4.2 t/m 4.9 en 5.3: 20 november 2024

11. GENERAL CLASSIFICATION FOR SUPPLY

Prescription only