1. NAAM VAN HET GENEESMIDDEL

Colecalciferol 1A Pharma 800 IE, zachte capsules
Colecalciferol 1A Pharma 3200 IE, zachte capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 20 micrograms colecalciferol (Vitamin D3), equivalent to 800 IU.
Each soft capsule contains 80 micrograms colecalciferol (Vitamin D3), equivalent to 3,200 IU.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

{[Nationally completed name] 800 IU soft capsules} are light yellow opaque, size 2, oval soft capsules. Capsule length is approximately 9.5 mm and width is approximately 5.9 mm.
{[Nationally completed name] 3,200 IU soft capsules} are yellow opaque, size 6, oval soft capsules. Capsule length is approximately 13.6 mm and width is approximately 8.4 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

800IU soft capsules

- Treatment of vitamin D deficiency (serum level < 25 nmol/L (<10 ng/mL)) in adults and adolescents.
- Prevention of vitamin D deficiency (serum level < 25 nmol/L (<10 ng/mL)) in adults with an identified risk.

3,200IU soft capsules

- Treatment of vitamin D deficiency (serum level < 25 nmol/L (<10 ng/mL)) in adults and adolescents.

{[Nationally completed name]} 800IU, 1,000IU and 3,200IU soft capsules are indicated in adolescents and adults.

4.2 Posology and method of administration

Posology

The dosage must be determined individually by the treating doctor depending on the extent of the necessary vitamin D supplementation. The dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), severity of the disease and patients response to treatment.
The patient's dietary habits should be carefully evaluated and artificially added vitamin D content of certain food types should be taken into consideration.

800IU and 3,200IU soft capsules

Treatment of vitamin D deficiency (serum levels < 25 nmol/l or < 10 ng/ml) in adults:
800IU-4,000IU/day

After the first month, a lower maintenance doses should be considered, dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient's response to treatment.

Prevention of vitamin D deficiency in adults with an identified risk:
800IU - 1,000IU/day.

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

Medical supervision is necessary as dose requirements may vary dependent on patient response (see section 4.4).

Special populations

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

Renal impairment
Colecalciferol is contraindicated in patients with severe renal impairment (see section 4.3).

Paediatric population

800IU and 3,200IU soft capsules

{[Nationally completed name]} should not be used in children under 12 years of age.

Treatment of vitamin D deficiency (serum levels < 25 nmol/l or < 10 ng/ml) in adolescents (12-18 years): 800-4000IU/day. The daily dose should not exceed 4000IU/day.

After the first month, a lower maintenance doses should be considered, dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient's response to treatment.

Method of administration

Oral administration
The capsules should be swallowed whole (not chewed) with water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Diseases/conditions associated hypercalcaemia and / or hypercalciuria.
- Calcium nephrolithiasis, nephrocalcinosis
- D- hypervitaminosis
- Severe renal impairment

4.4 Special warnings and precautions for use

Calcium levels
In the case of therapeutic treatment, the dose should be established on an individual basis for the patients by regular checking of plasma calcium levels. During treatment the serum calcium values, urinary calcium excretion and renal function must be monitored, especially in elderly patients who concomitantly take cardiac glycosides or diuretics (see section 4.5), and in the case of hyperphosphataemia, as well as for patients with an increased risk of lithiasis. In case of hypercalcaemia or hypercalciuria (exceeding 300 mg (7.5 mmol)/24 hours) treatment has to be discontinued. (see section 4.3). In case of impaired renal function, the dose should be reduced or the treatment discontinued.
During treatment proper calcium levels and adequate calcium intake preferably by nutrition should be ensured. Concomitant use of calcium containing products administered in large doses may increase the risk of hypercalcaemia.

Impaired renal function
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. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol may not be metabolised normally and {[Nationally completed name]} is contraindicated (see section 4.3).

Pseudohypoparathyroidism
Colecalciferol 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.

Sarcoidosis
Vitamin D3 should be prescribed with caution to patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active form. These patients should be monitored with regard to the calcium content in serum and urine.

Concomitant use of multivitamin products
The content of vitamin D in {[Nationally completed name]} should be considered when prescribing other medicinal products containing vitamin D. The concomitant use of multivitamin products and dietary supplements containing vitamin D should be avoided. This also applies to metabolites or analogues of vitamin D.

Paediatric population

800IU and 3,200 soft capsules
{[Nationally completed name]} should not be used in children under 12 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

Thiazide diuretics
Thiazide diuretics reduce the excretion of calcium with urine. Regular monitoring of the serum calcium level is necessary in the case of concomitant use with thiazide diuretics or with calcium containing products taken in large doses because of the increased risk of hypercalcaemia.

Digitalis and other cardiac glycosides
In cases of treatment with medicinal product containing digitalis and other cardiac glycosides, the administration of vitamin D may increase the risk of digitalis toxicity (arrhythmia). Strict medical supervision is needed and, if necessary monitoring of ECG and calcium.

Systemic corticosteroids
Systemic corticosteroids inhibit the absorption of calcium. Long-term use of corticosteroids may offset the effect of vitamin D.

Ion exchange resins, laxatives and orlistat
Simultaneous treatment with ion exchange resins (e.g. colestyramine), or laxatives (like paraffin oil) may reduce the gastrointestinal absorption of vitamin D. Orlistat may potentially impair the absorption of vitamin D as it is fat-soluble. Vitamin D may not be taken within 2 hours (before or after) any orlistat and vitamin D analog administration.

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

Anticonvulsants and barbiturates

Anticonvulsants, like phenytoin and barbiturates (e.g. primidone) may reduce the effect of vitamin D due to the activation of the microsomal enzyme system.

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

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

Ketoconazole
Ketoconazole may inhibit both synthetic and catabolic enzymes of vitamin D. Reductions in serum endogenous vitamin D concentrations have been observed following the administration of 300 mg/day to 1,200 mg/day ketoconazole for a week to healthy men. However, in vivo drug interaction studies of ketoconazole with vitamin D have not been investigated.

Rifampicin
Rifampicin may also reduce the effectiveness of vitamin D3 due to hepatic enzyme induction.

Isoniazid
Isoniazid may reduce the effectiveness of vitamin D3 due to inhibition of the metabolic activation of vitamin D.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of colecalciferol 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 hypercalcaemia 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 4,000IU/day vitamin D3. For treatment during pregnancy at higher doses, {[Nationally completed name]} is not recommended during pregnancy.

Breast-feeding
Vitamin D3 and its metabolites are excreted in breast milk. {[Nationally completed name]} 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
There are no data on the effect of colecalciferol on fertility. However, normal endogenous levels of vitamin D are not expected to have any adverse reactions on fertility.

4.7 Effects on ability to drive and use machines

{[Nationally completed name]} has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The frequency of possible adverse reactions listed below are defined as:
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

The adverse reactions are the result of overdose.

Immune system disorders:
Not known (cannot be estimated from the available data): Hypersensitivity reactions such as angio-oedema or laryngeal oedema

Metabolism and nutrition disorders:
Uncommon: Hypercalcaemia and hypercalciuria.

Gastrointestinal disorders:
Not known: Constipation, flatulence, nausea, abdominal pain, diarrhoea.

Skin and subcutaneous disorders:
Rare: Pruritus, rash and urticaria.

Dependent on dose and duration of treatment of serious and persistent hypercalcemia with its acute (heart rhythm disturbances, nausea, vomiting, psychiatric symptoms, loss of consciousness) and chronic (increased urination, increased thirst, loss of appetite, weight loss, kidney stones, kidney calcification, calcification may in tissues outside the bone) episodes occur.

Very rarely fatality has been described (see 4.4 "Special warnings and precautions for use" and 4.9 "overdose").

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 listed in Appendix V*.

4.9 Overdose

Symptoms of overdose

Overdose of the product may cause hypervitaminosis, hypercalcaemia and hyperphosphatemia. Acute or chronic overdose of vitamin D can cause hypercalcaemia. Symptoms of hypercalcemia are tiredness, headache, muscle and joint pain, muscle weakness, psychiatric symptoms (e.g., euphoria, dazedness, and disturbed consciousness), nausea, vomiting, lack of appetite, weight loss, thirst, polyuria, formation of renal calculi, nephrocalcinosis, extraosseous calcification and kidney failure, changes in ECG, arrhythmias, and pancreatitis. Chronic overdoses can lead to vascular and organ calcification as a result of hypercalcaemia.
Hypercalcaemia in extreme cases may lead to coma or even death.

Therapeutic measures in overdose
A specific antidote does not exist. As a first measure the vitamin D preparation should be discontinued; normalization of hypercalcemia due to vitamin D intoxication takes several weeks. At the same time, the use of thiazide diuretics, lithium, vitamin D and A as well as cardiac glycosides should also be discontinued. Depending on the degree of hypercalcaemia and on the patient's condition, e.g. in case of oligoanuria, haemodialysis (calcium-free dialysate) may be necessary. Graded according to the degree of hypercalcemia, the treatment is directed to symptoms. Rehydration and treatment with diuretics, e.g. furosemide to ensure adequate diuresis. In hypercalcemia biphosphonates or calcitonin and corticosteroids may be given.
Serum electrolyte levels, renal function and diuresis should be monitored. In severe cases ECG and central venous pressure monitoring may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues, colecalciferol ATC Code: A11CC05

Colecalciferol (vitamin D3) is formed in the skin on exposure to UVB light and converted into its biologically active form, 1,25-dihydroxycolecalciferol, in two hydroxylation steps, first in the liver (position 25) and then in the renal tissue (position 1). Along with parathormone and calcitonin, 1,25-dihydroxycolecalciferol has a considerable impact on the regulation of calcium and phosphate metabolism. In vitamin D deficiency the skeleton does not calcify (resulting in rickets) or decalcification of bones occurs (resulting in osteomalacia).

According to production, physiological regulation and mechanism of action, vitamin D3 is to be considered as precursor of a steroid hormone. In addition to physiological production in the skin, colecalciferol can be supplied via the diet or in the form of a medicinal product. Since in the latter case the product inhibition of cutaneous vitamin D synthesis is circumvented, overdose and intoxications may occur.

Epidemiological multinational investigations have revealed that from 52% (Holick et al., 2005) to 64% (Lips et al., 2006) of postmenopausal women taking medication for osteoporosis exhibited suboptimal levels of 25(OH)D - below 75 nmol/L (30 ng/mL). Optimal vitamin D repletion has been shown to be necessary to maximize the response to anti-resorbers in terms of both BMD changes and anti-fracture efficacy (Adami et al., 2009).

5.2 Pharmacokinetic properties

Absorption
Vitamin D is easily absorbed in the small intestine. Food intake potentially increases the absorption of vitamin D.

Distribution and biotransformation
Colecalciferol and its metabolites circulate in the blood bound to a specific globulin. Colecalciferol is converted in the liver by hydroxylation to 25-hydroxycolecalciferol. It is then further converted in the kidneys to 1,25- dihydroxycolecalciferol. 1,25-dihydroxycolecalciferol is the active metabolite responsible for increasing calcium absorption. Vitamin D, which is not metabolised, is stored in adipose and muscle tissues.

After a single oral dose of colecalciferol, the maximum serum concentrations of the primary storage form are reached after approximately 7 days. 25(OH)D3 is then slowly eliminated with an apparent half-life in serum of about 50 days.

Elimination
Colecalciferol and its metabolites are excreted mainly in the bile and faeces. A small percentage of an administered dose is found in urine.

Special population
A defect in the metabolism and excretion of vitamin D has been described in patients with chronic renal failure.

5.3 Preclinical safety data

Effects in non-clinical single and repeat-dose toxicity studies were observed only at exposures of high doses. At very high doses teratogenicity was observed in animal studies. Normal endogenous levels of cholecalciferol has no potential mutagenic activity (negative in Ames-test). Tests on carcinogenicity activity have not been conducted.

There is no further information of relevance to the safety assessment in addition to what is stated in other parts of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill
Butylhydroxytoluene (BHT) (E-321)
Medium chain triglyceride oil

Capsule shell
Gelatin (E-441)
Glycerol 99.5% (E-422)
Titanium dioxide (E-171)
Iron oxide yellow (E-172)
Water purified
In addition in {[Nationally completed name] 1,000 IU soft capsules}:
Iron oxide red (E-172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Opaque PVC/PVdC-Alu blister

{[Nationally completed name] 800 IU soft capsules} is available in packs containing 28, 30, 80 or 90 soft capsules.
{[Nationally completed name] 3,200 IU soft capsules} is available in packs containing 7, 30 or 90 soft capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

1 A Pharma GmbH
Industriestraße 18
83607 Holzkirchen
Duitsland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Colecalciferol 1A Pharma 800 IE, zachte capsules	RVG 128772
Colecalciferol 1A Pharma 3200 IE, zachte capsules	RVG 128773

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 5 oktober 2022

10. DATUM VAN HERZIENING VAN DE TEKST