SUMMARY OF PRODUCT CHARACTERISTICS

Product Summary

1 NAME OF THE MEDICINAL PRODUCT

Cholecalciferol Pharmemma 1.000 IE, zachte capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

25 micrograms Cholecalciferol (vitamin D3), equivalent to 1,000 IU

Excipient(s) with known effect:

Each capsule also contains 16.5 milligrams of sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule
Green coloured clear transparent round shaped gelatin capsule with a clear, colourless liquid fill with approximate dimensions 7.36 mm x 6.27 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Vitamin D deficiency (serum 25(OH)D < 25 nmol/l) in adults, the elderly and adolescents.
Prevention of vitamin D deficiency in high-risk patients in adults and the elderly.
As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.

4.2 Posology and method of administration

Posology

Adults

Dose should be established on an individual basis depending on the extent of the necessary vitamin D supplementation. Cholecalciferol Pharmemma 1,000 IU capsules are suitable for daily vitamin D supplementation. Dosage should be established by a physician.

Osteomalacia in adults: The dosage should be established by the treating physician. Certain populations are at high risk of vitamin D deficiency, and may require higher doses and monitoring of serum 25(OH)D.

Osteoporosis: For the adjunct therapy of osteoporosis a daily
doses equivalent of 2,000 IU vitamin D should be considered in fragile elderly patients who are at particular risk of falls and fractures. Recommended dose Cholecalciferol Pharmemma 1,000 IU soft capsules: 2 capsules/daily. Patients should receive supplemental calcium if intake from diet is inadequate.

Vitamin D deficiency (serum levels < 25 nmol/l or < 10 ng/ml) in adults and the elderly: 800 IU-4,000 IU daily for up to 12 weeks.
Recommended dose: 1 capsule/daily. Higher doses should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment.

Vitamin D insufficiency (serum levels 25-50 nmol/l or 10-20 ng/ml) in adults and the elderly:
AND
Long term maintenance therapy following treatment of deficiency in adults and the elderly:
AND
Prevention of vitamin D deficiency:
800-1600 IU daily.
Recommended dose Cholecalciferol Pharmemma 1,000 IU soft capsules: 1 capsule/daily.

Adolescents

Treatment of vitamin D deficiency in adolescents (13 – 17 years): 800-1,000 IU daily depending on the severity of the disease and the patient`s response to treatment. Recommended dose Cholecalciferol Pharmemma 1,000 IU soft capsules: 1 capsule/daily.
Should only be given under medical supervision.
Alternatively, national posology recommendations in treatment of vitamin D deficiency can be followed.

The recommended doses are not all possible using this product, however, products with dosage lower than 1,000 IU are available.

Hepatic impairment: No dose adjustment is necessary for patients with hepatic impairment.
During vitamin D therapy, calcium and phosphor intake has fundamental significance with respect to the success of the treatment.

Renal impairment: Cholecalciferol Pharmemma Capsules must not be used in patients with severe renal impairment (see section 4.3).

Before starting the vitamin D therapy, the patient's dietary habits should be carefully evaluated by the doctor and artificially added vitamin D content of certain food types should be taken into consideration.

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

Paediatric population

Prevention of vitamin D deficiency: The efficacy and safety of Vitamin D_3 Capsules has not been established in children and adolescents < 18 years. The use is therefore not recommended.

Vitamin D_3 Capsules should not be used in children under 12 years.

Method of administration

Oral

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

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 long-term treatment, serum calcium level, urinary calcium excretion and renal function should be monitored by measuring the serum creatinine level. Monitoring is especially important for 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 hypercalciuria (exceeding 300 mg (7.5 mmol)/24 hours) or signs of impaired renal function the dose should be reduced or the treatment discontinued.

Vitamin D should be used with caution in patients with impaired renal function. In this case monitoring of calcium and phosphate levels is necessary, and the risk of soft tissue calcification should be taken into consideration. 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.

Cholecalciferol Pharmemma Capsules 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.

Cholecalciferol Pharmemma Capsules should be used with caution in patients with sarcoidosis because of the risk of vitamin D's increased transformation to its active form. Blood and urine calcium levels should be regularly monitored in these patients.

In the case of concomitant use with other medicinal product containing vitamin D, its vitamin D content should be taken into consideration. The concomitant use of multivitamin products and dietary supplements containing vitamin D should be avoided.

Medicinal products having effect through the inhibition of bone resorption decrease the calcium amounts derived from bone. In order to avoid this, as well as concomitantly to treatment with medicines enhancing bone development, it is necessary to ensure proper calcium levels and if needed take vitamin D.

This product contains sorbitol liquid partially dehydrated. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

Concomitant use with calcium containing products administered in large doses may increase the risk of hypercalcaemia.

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.

Systematic corticosteroids inhibit the absorption of calcium. Long-term use of corticosteroids may offset the effect of vitamin D. The effects of digitalis and other cardiac glycosides may be accentuated with the oral administration of calcium combined with Vitamin D. Strict medical supervision is needed and, if necessary monitoring of ECG and calcium.

Concomitant use of calcitonin, etidronate, gallium nitrate, pamidronate or plicamycin with vitamin D may antagonise the effect of these products in hypercalcaemia treatment.

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

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.

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 magnesium (like antacids) may not be taken during long-terms high dose vitamin D treatment because of the risk of hypermagnesaemia.

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

4.6 Fertility, Pregnancy and lactation

<u>Pregnancy</u>

The recommended daily intake for pregnant women is 400 IU, however, in women who are considered to be vitamin D deficient a higher dose may be required. During pregnancy women should follow the advice of their medical practitioner as their requirements may vary depending on the severity of their disease and their response to treatment.
Daily vitamin D3 intake during pregnancy may not exceed 600 IU. Overdoses of vitamin D have been shown to have teratogenic effects in animal experiments.
In pregnant women, overdosage of vitamin D3 should be avoided, since prolonged hypercalcaemia has been sometimes associated with retardation of physical and mental development, supravalvular aortic stenosis and retinopathy in the child.

Breastfeeding

Vitamin D and its metabolites are excreted in breast milk. Overdose in infants induced by nursing mothers has not been observed, however, when prescribing additional vitamin D to a breast-fed child the practitioner should consider the dose of any additional vitamin D given to the mother.

Fertility
There are no data on the effect of Vitamin D on fertility. However, normal endogenous levels of vitamin D are not expected to have any adverse effects on fertility.

4.7 Effects on the ability to drive and use machines

Cholecalciferol Pharmemma Capsules has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The frequency of possible side effects 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)

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.

Skin and subcutaneous disorders:
Rare: 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 via het Nederlands Bijwerkingen Centrum Lareb, website www.lareb.nl.

4.9 Overdose

Overdose of the product may cause hypervitaminosis, hypercalcaemia and hyperphosphatemia. Symptoms of hypercalcaemia: anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, confusion, polydipsia, polyuria, bone pain, calcification in the kidneys, kidney stones, vertigo, and cardiac arrhythmia in severe cases. Hypercalcaemia in extreme cases may lead to coma or even death. Persistently high levels of calcium may cause irreversible renal impairment and soft tissue calcification.

Treatment of hypercalcaemia: treatment with vitamin D (and calcium) should be discontinued. At the same time, the use of thiazide diuretics, lithium, vitamin D and A as well as cardiac glycosides should also be discontinued. In the case of patients with impaired consciousness gastric emptying is also necessary. Rehydration and mono- or combined therapy with loop diuretics, bisphosphonates, calcitonin and corticosteroids may be used depending on the severity of the overdose. 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, ATC code: A11CC05

In its biologically active form, vitamin D stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue.

In the small intestine it promotes rapid and delayed calcium uptake. The passive and active transport of phosphate is also stimulated.
In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular resorption. The production of parathyroid hormone (PTH) in the parathyroids is inhibited directly by the biologically active form of vitamin D. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active vitamin D.

5.2 Pharmacokinetic properties

<u>Absorption</u>
Fat-soluble vitamin D3 is absorbed through the small intestine in the presence of bile acids with the help of micellum and gets into the blood through lymphatic circulation.

<u>Distribution</u>

Following absorption, vitamin D3 enters the blood as part of chylomicrons. Vitamin D3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D3 at these sites for later release into the circulation. Circulating vitamin D3 is bound to vitamin D-binding protein.

Biotransformation
Vitamin D3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D3 undergoes glucuronidation prior to elimination.

Elimination Vitamin D and its metabolites are excreted in faeces and urine.

5.3 Preclinical safety data

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. There is no further information of relevance to the safety assessment in addition to what is stated in other parts of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Medium chain triglycerides
Vitamin E Acetate (α-Tocopheryl Acetate) *(E307)*

Capsule Shell:
Gelatin *(E441)*
Glycerol *(E422)*
Sorbitol liquid partially dehydrated
Brilliant Blue *(E133)*
Quinoline yellow *(E104)*
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PVdC-Al blisters:
36 months

HDPE Containers:
24 months

HDPE Containers: Once opened use within 105 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

[HDPE Containers with polypropylene cap]
20 soft capsules
30 soft capsules
50 soft capsules

[White opaque PVC/PVdC-Al blisters]
30 soft capsules
60 soft capsules
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. MARKETING AUTHORISATION HOLDER

Pharmemma Limited
Unit 2, Ashbourne Manufacturing Park
Ashbourne
Co. Meath
Ierland

8. MARKETING AUTHORISATION NUMBER

RVG 127291

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Datum van eerste verlening van de vergunning: 20 oktober 2020

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 6.3: 11 oktober 2022