SUMMARY OF PRODUCT CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDEL

Cholecalciferol Acure 20.000 IE zachte capsules
Cholecalciferol Acure 25.000 IE zachte capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 micrograms of cholecalciferol (vitamin D_3, equivalent to 20 000 IU).
Each capsule contains 625 micrograms of cholecalciferol (vitamin D_3, equivalent to 25 000 IU).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

20 000 IU capsule, soft
Transparent, blue, round with 7.2 mm of diameter, soft capsules with a seam in the middle, filled with light yellow viscous liquid.

25 000 IU capsule, soft
White to almost white, oval with 12 mm of length and 6.7 mm of thickness, soft capsules with a seam in the middle, filled with light yellow viscous liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Initial treatment of clinically relevant vitamin D deficiency (serum levels < 25 nmol/l or < 10 ng/ml) in adults.

<Proposed name> 20 000 IU and 25 000 IU soft capsules are indicated in adults.

4.2 Posology and method of administration

Posology

Dose should be established on an individual basis depending on the extent of the necessary vitamin D supplementation. The dosage must be determined individually by the treating doctor depending on the extent of the necessary vitamin D supplementation.
The patient's dietary habits should be carefully evaluated and artificially added vitamin D content of certain food types should be taken into consideration.

Initial treatment of clinically relevant vitamin D deficiency (serum levels < 25 nmol/l or < 10 ng/ml) in adults:
1 capsule of 20 000 IU /week for up to 4-5 weeks
1 capsule of 25 000 IU /week for up to 4 weeks

After first month, a lower maintenance dose 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.

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

followed. The duration of use is usually limited to the first month of treatment, depending on the doctor's decision. Medical supervision is necessary as dose requirements may vary dependent on patient response (see section 4.4).

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

Renal impairment
<Proposed name> must not be used in patients with severe renal impairment (see section 4.3).

Paediatric population
The strength of 20 000 IU and 25 000 IU soft capsules per week are not suitable for the use in children and adolescents up to 18 years because studies on the safe use of very high doses in children and adolescents are too limited. However, products with a strength lower than 20 000 IU and 25 000 IU may also be available.
Method of administration
The capsule should be swallowed whole with water, preferably with the main meal of the day.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Monitoring
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 initial 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 or immobilized patients. 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.

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 cholecalciferol may not metabolised normally and high-doses of cholecalciferol must not be used (see section 4.3).

Pseudohypoparathyroidism
Vitamin D 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 D 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 this medicinal product should be considered when prescribing other medicinal products containing vitamin D, or its metabolites or analogues. The concomitant use of

multivitamin products and dietary supplements containing vitamin D should be avoided.

Intake of calcium
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.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Ion exchange resins and laxatives
Simultaneous treatment with ion exchange resins (e.g. colestyramine), or laxatives (like paraffin oil) may reduce the gastrointestinal absorption of vitamin D.

Orlistat
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 analogue administration.

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

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.

Rifampicin
Rifampicin may also reduce the effectiveness of vitamin D_3 due to hepatic enzyme induction.

Isoniazid
Isoniazid may reduce the effectiveness of vitamin D_3 due to inhibition of the metabolic activation of vitamin D.

Pharmacodynamic interactions

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 drugs 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.

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

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

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

4.6 Fertility, pregnancy and lactation

During pregnancy and breastfeeding, this high dosed product is not recommended, and a lower dosed product should be used. Adequate vitamin D intake is necessary during pregnancy and breast-feeding. The recommended daily intake level for vitamin D during pregnancy and lactation should follow national guidelines.

Pregnancy
During pregnancy, the daily intake should not exceed 4,000 IU vitamin D (100 µg cholecalciferol).

Overdose of vitamin D must be avoided during pregnancy, as prolonged hypercalcaemia can lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child. Studies in animals have shown reproductive toxicity of high doses of vitamin D (see section 5.3).

Breast-feeding
High-dose vitamin D should not be used during breast-feeding. Vitamin D and its metabolites pass into breast milk. If treatment with <Proposed name> is clinically indicated during breast-feeding, this should also 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

Vitamin D has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Listing of adverse reactions
The frequency of possible side effects listed below are defined as:
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1000 to <1/100)
Rare (≥ 1/10 000 to <1/1000)
Very rare (<1/10 000)
Not known (cannot be estimated from the available data)

The side effects are the result of overdose.

I*mmune 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.

Hypercalcaemia
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 section 4.4 and 4.9).

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. In isolated cases their course has been described as fatal. 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, ATC code: A11CC05

Mechanism of action
Cholecalciferol (vitamin D_3) is formed from 7-dehydrocholesterol in the skin on exposure to UVB light and converted into its biologically active form, 1,25-dihydroxycholecalciferol, 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- dihydroxycholecalciferol 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 D_3 is to be considered as precursor of a steroid hormone. In addition to physiological production in the skin,

cholecalciferol can be supplied via the diet or in the form of a drug. Since in the latter case the product inhibition of cutaneous vitamin D synthesis is circumvented, overdose and intoxications may occur.

Fish liver oil and fish are particularly rich in vitamin D; small amounts are found in meat, egg yolk, milk, dairy products and avocado.

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

Studies of radioactively labelled D_3 find the whole body half-life of vitamin D_3 molecules to be approximately 62 days.

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

5.3 Preclinical safety data

Effects in non-clinical single and repeat-dose toxicity studies have been observed only at exposures of high doses. At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. Normal endogenous levels of cholecalciferol have 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill:
Triglycerides, medium chain
All-rac-α-tocopheryl acetate (E307)

Capsule shell:
Gelatine (E441)
Glycerol (E422)
Patent blue V (E131) *(only applicable 20 000 IU strength)*
Titanium dioxide (E171) *(only applicable 25 000 IU strength)*
Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

27 months

6.4 Special precautions for storage

Do not store above 30 °C.
Store in the original package to protect from light and moisture.

6.5 Nature and contents of container

Al/PVC/PVDC blisters.

20 000 IU
Box containing 6, 20, 50 or 100 soft capsules

25 000 IU
Box containing 20, 48, 50 or 100 soft capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Acure Pharmaceuticals Limited
Unit D - Stephenstown Industrial Park, Balbriggan
K32 VR92, Co. Dublin
Ierland

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

RVG 128780
RVG 128782

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

Datum van verlening van de vergunning: 1 december 2022

10. DATUM VAN HERZIENING VAN DE TEKST