Cholecalciferol

D-Cure® Rx

25.000IU Oral Solution

Vitamin

1. NAME OF THE MEDICINAL PRODUCT

Cholecalciferol (D-Cure) 25,000 IU oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution (1 single-dose oral solution in ampoule) contains 0.625 mg cholecalciferol, equivalent to 25,000 IU vitamin D.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear, slightly yellow, oily liquid with an orange odour

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the prevention and treatment of vitamin D deficiency.

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

Paediatrics:

- Prevention of deficiency 0-1 years 25000 IU (1 single-dose oral solution in ampoule) every 8 weeks
- Prevention of deficiency 1-18 years 25000 IU (1 single-dose oral solution in ampoule) every 6 weeks
-Treatment of deficiency 0-18 years 25000 IU (1 single-dose oral solution in ampoule) once every 2 weeks for 6weeks (followed by maintenance therapy of 400-1000 IU/day)

Administration to children:

In children, Cholecalciferol (D-Cure) can be mixed with a small amount of children's foods, yogurt, milk, cheese or other dairy products. The parents should be warned not to mix Cholecalciferol (D-Cure) into a bottle of milk or container of soft foods in case the child does not consume the whole portion, and does not receive the full dose. The parents should ensure that their child takes the entire dose. For children who are not breast-feeding, the prescribed dose should be administered with a meal.

Adults:

- Prevention of vitamin D deficiency 25000 IU/month (1 single-dose oral solution in ampoule)
- Treatment of vitamin D deficiency (<25 ng/ml) 50000 IU/week (2 single-dose oral solution in ampoule) for 6-8weeks, followed by maintenance therapy (1400-2000 IU/day may be required; follow-up 25(OH)D measurements should be made approximately three to four months after initiating maintenance therapy to confirm that the target level has been achieved)

- As an adjunct to specific therapy for osteoporosis: 25000 IU/month (1 single-dose oral solution in ampoule)

Administration to adults:
Cholecalciferol (D-Cure) is an oral solution packaged in single-dose container. The content of the single-dose oral solution (in ampoule) is to be emptied directly into the mouth and swallowed orally. To help the patient, the full content of the single-dose oral solution (in ampoule) may be emptied onto a spoon and taken orally. D-Cure can also be taken by mixing with a small amount of cold or lukewarm food immediately prior to use. Cholecalciferol (D-Cure) is only for oral use.

Certain populations are at high risk of vitamin D deficiency, and may require higher doses and monitoring of serum 25(OH)D:
- Institutionalised or hospitalised individuals
- Dark skinned individuals
- Individuals with limited effective sun exposure due to protective clothing or consistent use of sunscreens
- Obese individuals
- Patients being evaluated for osteoporosis
- Use of certain concomitant medications (e.g., anticonvulsant medications, glucocorticoids)
- Patients with malabsorption, including inflammatory bowel disease and coeliac disease
- Those recently treated for vitamin D deficiency, and requiring maintenance therapy.

Special populations
Renal impairment
Cholecalciferol (D-Cure) should not be used in combination with calcium in patients with severe renal impairment.

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

Pregnancy and breastfeeding:
- The high strength formulation is not recommended

Method of administration
Patients should be advised to take D-Cure preferably with meal (see section 5.2 Pharmacokinetic properties - "Absorption").

See also section 6.6, Special precautions for handling and disposal.

4.3 Contraindications
• Hypersensitivity to the active substance(s) or to any of the excipients.
• Hypercalcaemia and/or hypercalciuria.
• Nephrolithiasis and/or nephrocalcinosis
• Serious renal impairment
• Hypervitaminosis D
• Pseudohypoparathyroidism as the vitamin D requirement may be reduced due to phases of normal vitamin D sensitivity, involving the risk of prolonged overdose. Better-regulatable vitamin D derivatives are available for this.

4.4 Special warnings and precautions for use

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.

Caution is required in patients receiving treatment for cardiovascular disease (see section 4.5 Interaction with other medicinal products and other forms of interaction - cardiac glycosides including digitalis).

Cholecalciferol (D-Cure) should be prescribed with caution in patients with sarcoidosis, due to a possible increase in the metabolism of vitamin D in its active form. In these patients the serum and urinary calcium levels should be monitored.

Allowances should be made for the total dose of vitamin D in cases associated with treatments already containing vitamin D, foods enriched with vitamin D, cases using milk enriched with vitamin D, and the patient's level of sun exposure.

There is no clear evidence for causation between vitamin D supplementation and renal stones, but the risk is plausible, especially in the context of concomitant calcium supplementation. The need for additional calcium supplementation should be considered for individual patients. Calcium supplements should be given under close medical supervision.

Oral administration of high-dose vitamin D (500,000 IU by single annual bolus) was reported to result in an increased risk of fractures in elderly subjects, with the greatest increase occurring during the first 3 months after dosing.

In patients with idiopathic infantile hypercalcaemia (e.g. CYP24A1 mutation or SLC34A1 mutation), the risk of hypercalcaemia and secondary effects (e.g. hypercalciuria, nephrocalcinosis, nephrolithiasis) is increased due to accumulation of active vitamin D. Idiopathic infantile hypercalcaemia may be asymptomatic and undiagnosed at the beginning of vitamin D therapy and may be unmasked and become clinically apparent after vitamin D supplementation.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of anticonvulsants (such as phenytoin) or barbiturates (and possibly other drugs that induce hepatic enzymes) may reduce the effect of vitamin D_3 by metabolic inactivation.

In cases of treatment with thiazide diuretics, which decrease urinary elimination of calcium, monitoring of serum calcium concentration is recommended.

Concomitant use of glucocorticoids can decrease the effect of vitamin D.

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, together with serum calcium concentration and electrocardiographic monitoring if necessary.

Simultaneous treatment with ion exchange resin such as cholestyramine, colestipol hydrochloride, orlistat or laxative such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.

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.

4.6 Fertility, pregnancy and lactation

In pregnancy and lactation, the high strength formulation is not recommended and a low strength formulation should be used.

Pregnancy

There are no or limited amount of data from the use of cholecalciferol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). 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 (up to 2000 IU/day).

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 vitamin D and its metabolites are excreted in breast milk. Overdose of vitamin D must be avoided during pregnancy, as prolonged hypercalcemia can lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child.

Breast-feeding

Vitamin D can be prescribed while the patient is breast-feeding if necessary. This supplementation does not replace the administration of vitamin D in the neonate.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Injury, poisoning and procedural complications are the result of an incorrect route of drug administration, accidental overdose or exposure, or underdose.

The following adverse events can be observed (based on the post-marketing data source):

Psychiatric disorders
Confusional state, aggression, insomnia

Gastrointestinal disorders
Nausea, abdominal pain, diarrhoea, vomiting, gastrointestinal disorder, dyspepsia

Nervous system disorders
Dizziness, flushing

Metabolism and nutrition disorders
Hypercalcaemia, hypercalciuria, decreased appetite, tetany

Skin and subcutaneous disorders:
Pruritus, urticaria, rash, hyperhidrosis

The side effects are the result of overdose.
Depending on the dose and duration of treatment, severe and prolonged hypercalcaemia with its acute (cardiac arrhythmias, nausea, vomiting, psychic symptoms, disturbances of consciousness) and chronic (increased urgency to urinate, increased thirst, loss of appetite, weight loss, kidney stones, kidney calcification, calcification in tissues outside the skeleton) consequences can occur. A fatal outcome has been reported in very rare cases. (see also section 4.4 'Special warnings and precautions for use' as well as section 4.5 'Interaction with other medicinal products and other forms of interaction'. Furthermore, refer also to section 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 advice to report any suspected adverse reactions to the Product Registration Holder.

4.9 Overdose

Symptoms of overdose

Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) have a relatively low therapeutic index. The threshold for vitamin D intoxication is between 40,000 and 100,000 IU daily for 1 to 2 months in adults with normal parathyroid function. Infants and small children may react sensitively to far lower concentrations. Therefore, it is warned against intake of vitamin D without medical supervision.

Overdose leads to increased serum and urinary phosphorus levels, as well as hypercalcaemic syndrome and consequently calcium deposits in the tissues and above all in the kidneys (nephrolithiasis, nephrocalcinosis) and the vessels.
Discontinue Cholecalciferol (D-Cure) when calcaemia exceeds 10.6 mg/dl (2.65 mmol/l) or if the calciuria exceeds 300 mg/24 hours in adults or 4-6 mg/kg/day in children.

Chronic overdosage may lead to vascular and organ calcification, as a result of hypercalcaemia.
The symptoms of intoxication are little characteristic and manifest as nausea, vomiting, initially also diarrhoea, later constipation, loss of appetite, weariness, headache, muscle pain, joint pain, muscle weakness, persistent sleepiness, azotaemia, polydipsia and polyuria and, in the final stage, dehydration. Typical biochemical findings include hypercalcaemia, hypercalciuria, as well as increased serum 25 hydroxycholecalciferol concentrations.

Treatment of overdose

Symptoms of chronic vitamin D overdosage may require forced diuresis as well as administration of glucocorticoids or calcitonin.
Overdosage requires measures for treating the - often persisting and under certain circumstances life-threatening - hypercalcaemia.
The first measure is to discontinue the vitamin D preparation; it takes several weeks to normalise hypercalcaemia caused by vitamin D intoxication.
Depending on the degree of hypercalcaemia, measures include a diet that is low in calcium or free of calcium, abundant liquid intake, increase of urinary excretion by means of the drug furosemide, as well as the administration of glucocorticoids and calcitonin.
If kidney function is adequate, calcium levels can be reliably lowered by infusions of isotonic sodium chloride solution (3-6 liters in 24 hours) with addition of furosemide and, in some circumstances, also 15 mg/kg body weight/hour sodium edetate accompanied by continuous calcium and ECG monitoring. In oligoanuria, in contrast, haemodialysis (calcium-free dialysate) is necessary.
No special antidote exists.
It is recommended to point out the symptoms of potential overdose to patients under chronic therapy with higher doses of vitamin D (nausea, vomiting, initially also diarrhoea, later constipation, anorexia, weariness, headache, muscle pain, joint pain, muscle weakness, persistent sleepiness, azotaemia, polydipsia and polyuria).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D, cholecalciferol

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 D3. 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

The pharmacokinetics of vitamin D is well known.

Absorption
Vitamin D is well absorbed from the gastro-intestinal tract in the presence of bile, so the administration with the major meal of the day might therefore facilitate the absorption of vitamin D.

Distribution and biotransformation
It is hydroxylated in the liver to form 25-hydroxy-cholecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1, 25-dihydroxycholecalciferol (calcitriol).

Elimination
The metabolites circulate in the blood bound to a specific α - globin, vitamin D and its metabolites are excreted mainly in the bile and faeces.

Characteristics in Specific Groups of Subjects or Patients
A 57% lower metabolic clearance rate is reported in subjects with renal impairment as compared with that of healthy volunteers.
Decreased absorption and increased elimination of vitamin D occurs in subjects with malabsorption. Obese subjects are less able to maintain vitamin D levels with sun exposure, and are likely to require larger oral doses of vitamin D to replace deficits.

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. At doses equivalent to those used therapeutically, cholecalciferol has no teratogenic, carcinogenic or mutagenic activity.

There is further no information of relevance to the safety assessment in addition to what is stated in other parts of the product insert.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tocopherol acetate, Polyglyceryl
oleate (E475), Olive oil,refined
Sweet orange peel oil.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Transparent PVC/PVDC/PE ampoules.
Original Pack with 4 ampoules or 12 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

6.7 Manufactured by:
SMB Technology S.A.
Rue du Parc Industriel 39 B-6900
Marche-en-Famenne, Belgium

For:
Laboratoires SMB S.A.
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Belgium

Name and Address of Product Registration Holder:

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7 DATE OF REVISION OF THE TEXT

March 2025

8 Philippines Local Specific Requirements

Date of First Authorization in Philippines:
07 September 2018

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR reporting statement: For suspected adverse drug reactions, report to FDA. (Applicable to patients based in the Philippines only. Patients based in Malaysia and Singapore shall report any side effects or adverse drug reactions to directly to NPRA and HSA, respectively.)

Seek medical attention immediately at the first sign of any adverse drug reaction.