D_3-Vicotrat®

1. NAME OF THE MEDICINAL PRODUCT

D_3-Vicotrat®

100 000 IU/1 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ampoule with 1 ml of solution for injection contains:
2.5 mg cholecalciferol (vitamin D_3) corresponding to 100 000 IU

Excipient with known effect: sorbitol, liquid 70%

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection for intramuscular use

Clear to opalescent, slightly yellowish solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of vitamin D deficiency symptoms due to malabsorption, e.g. caused by chronic intestinal diseases, biliary hepatocirrhosis, extended stomach or intestines resections, if an oral therapy is impossible or ineffective.

4.2 Posology and method of administration

Posology

Adults

Prophylaxis due to malabsorption: ½ - 1 ampoule (50 000 to 100 000 IU of vitamin D) as a single dose in individual intervals (normal case: every 3 months).
The serum calcium level should be monitored every 3 - 6 months and the dose should be adjusted according to the values.

Method of administration

The injection solution is administered by deep intramuscular injection.

In case of an intravenous injection the oily part of the solution can lead to embolisms and the solubilizer to haemolysis depending on the applied dosage.

Paediatric Population

There is no expert knowledge with children.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- hypercalcemia and/or hypercalciuria
- pregnancy and lactation.

4.4 Special warnings and precautions for use

D_3-Vicotrat should not be administered to patients
- with a tendency to the formation of kidney stones containing calcium, also in the anamnesis;
- with pseudohypoparathyroidism (the demand of vitamin D can be reduced due to the temporarily normal vitamin D sensitivity with the risk of a long-lasting overdose). In this case easily controllable vitamin D derivatives are available.

D_3-Vicotrat should be administered only with caution to patients
- with impaired renal calcium and phosphate excretion, in case of treatment with benzothiadiazine derivatives and immobilized patients, e.g. due to a cast (risk of hypercalcemia, hypercalciuria);
- suffering from sarcoidosis because the risk of transformation of vitamin D into its active metabolites is increased.

The calcium levels in serum and urine should be monitored in these patients.

During a long-term therapy with D_3-Vicotrat the calcium levels in serum and urine should be monitored every 3 to 6 months, and the kidney function should be checked by measuring the serum creatinine. This check is particularly important in older patients and during a concomitant therapy with cardiac glycosides or diuretics. In case of hypercalcemia or symptoms of an impaired kidney function the dosage must be reduced or the therapy be stopped. It is recommended to reduce the dosage or to interrupt the therapy if the calcium level in the urine exceeds 7.5 mmol/24 hours (300 mg/24 hours).

If other drugs containing vitamin D are prescribed, the dosage of vitamin D from D_3-Vicotrat must be taken into account. Additional administration of vitamin D or calcium should only be carried out under medical supervision. In such cases the calcium levels in serum and urine must be monitored.

In patients with renal insufficiency, that are treated with D_3-Vicotrat, the effect on the calcium and phosphate level should be monitored.

This medicine contains 31 mg sorbitol in each ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

Phenytoine or barbiturates can reduce the effect of vitamin D_3.

Thiazide diuretics can lead to hypercalcemia due to the reduction of the renal calcium excretion. Therefore, the calcium levels in serum and urine should be monitored during a long-term therapy.

The simultaneous administration of glucocorticoids can reduce the effect of vitamin D_3.

The toxicity of cardiac glycosides may be raised due to an increase of the calcium level during the therapy with vitamin D (risk of cardiac dysrhythmia). In these patients ECG and calcium level in serum and urine should be monitored.

Only in exceptional cases and under serum calcium controls D_3-Vicotrat should be combined with metabolic products or analogues of vitamin D.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation
Overdose of vitamin D in pregnancy must be prevented since long-lasting hypercalcemia can lead to physical and mental retardation as well as to congenital heart and eye diseases of the child. Therefore D_3-Vicotrat may not be used during pregnancy and lactation.

If a vitamin D supplement should be required, a drug with a lower cholecalciferol content than D_3-Vicotrat should be chosen.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed.

4.8 Undesirable effects

The side effects of vitamin D result from hypercalcemia due to overdose. Depending on dosage and duration of the therapy a severe and long-lasting hypercalcemia can appear with acute symptoms (arrhythmia, nausea, vomiting, psychic symptoms, and impaired consciousness) and chronic symptoms (polyuria, polydipsia, anorexia, weight loss, kidney stone formation, nephrocalcinosis, extraosseous calcifications). In individual cases lethal courses have been described (see also section 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 to Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, Website: www.bfarm.de.

4.9 Overdose

Symptoms of overdose
Ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) have a relative low therapeutic index. In adults with normal parathyroid function the threshold for vitamin D intoxication is between 40 000 and 100 000 IU per day during 1 to 2 months. Babies and infants may react severely to far lower concentrations. Therefore, vitamin D should not be administered without medical control.

Overdose leads to an increase of phosphorus in serum and urine and to the hypercalcemia syndrome, later also to calcium deposit in the tissues, primarily in the kidneys (nephrolithiasis, nephrocalcinosis) and the vessels.

The symptoms of an intoxication are nonspecific and may appear as nausea, vomiting, at first often as diarrhoea, later on as obstipation, anorexia, weakness, headache, muscle and joint pain, muscle weakness as well as persistent drowsiness, azotaemia, polydipsia and polyuria, finally as exsiccosis. Typical laboratory test results are hypercalcemia, hypercalciuria as well as increased serum levels of 25-hydroxycholecalciferol.

Treatment of overdose
In case of an overdose measures for the treatment of the often long-lasting and potentially threatening hypercalcemia are required.

The first measure is to stop the administration of the vitamin D product; a normalization of the hypercalcemia due to vitamin D intoxication lasts for several weeks.

Graduated according to the extent of the hypercalcemia low calcium or calcium free nutrition, plenty intake of fluids, forced diuresis by means of furosemide as well as the administration of glucocorticoids and calcitonine may be applied.

Infusions of isotonic NaCl solution (3-6 l in 24 hour) with addition of furosemide as well as possibly 15 mg/kg BW sodium edetate under continuous calcium and ECG-control have a quite reliable calcium lowering effect in patients with a sufficient kidney function. Haemodialysis (calcium free dialysis fluid) is indicated in case of oligouria.

A special antidote does not exist.

It is recommended to inform patients with long-term treatment with higher vitamin D doses about the symptoms of a possible overdose (nausea, vomiting, at the beginning often diarrhoeas, later obstipation, anorexia, weakness, headache, muscle and joint pain, muscle weakness, drowsiness, azotaemia, polydipsia and polyuria).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamins, vitamin D and analogues

ATC-Code: A11CC05

Cholecalciferol (vitamin D_3) is synthesized in the skin under the influence of UV rays and is then metabolized in two hydroxylation steps, at first in the liver (position 25) and next in the kidney tissue (position 1) into the biologically active form 1,25-dihydroxy-cholecalciferol. 1,25-dihydroxy-cholecalciferol is essentially involved in the regulation of the calcium and phosphate balance together with parathyroid hormone and calcitonine. In case of a vitamin D deficiency the calcification of the skeleton does not occur (rickets) or bone decalcification may result (osteomalacia).

According to the formation, physiological regulation and mode of action the so-called vitamin D_3 is to be considered as precursor of a steroid hormone. Besides the physiological production in the skin cholecalciferol can be supplied with nutrition or as drug product. When administered as a drug product the physiological inhibition of the cutaneous vitamin D synthesis will be avoided and overdoses and intoxications may occur. Ergocalciferol (vitamin D2) is formed in plants. In humans it is metabolically activated like cholecalciferol and has qualitatively and quantitatively similar effects.

Occurrence and coverage of need
Fish liver oil and fish are particularly rich in vitamin D, small quantities are found in meat, egg yolk, milk, dairy products and avocado.

The daily demand for adults is 5 µg, corresponding to 200 IU. Healthy adults can cover their requirements at sufficient sun exposure by own synthesis. The supply by food is only of minor importance. However, it can be important in critical conditions (climate, way of life).

Deficiency symptoms
Deficiency symptoms may appear for instance in immature premature babies, in infants exclusively breastfed for more than six months without supplementary food containing calcium, and in children on strict vegetarian diet. The rare vitamin D deficiency in adults may be caused by inadequate alimentary supply, insufficient UV exposure, malabsorption and maldigestion, hepatocirrhosis as well as renal insufficiency.

5.2 Pharmacokinetic properties

Absorption
In alimentary doses vitamin D is almost completely absorbed from the nutrition together with nutrition lipids and bile acids. Higher doses are absorbed with a resorption rate of about 2/3. In the skin vitamin D is synthesized under the influence of UV light from 7-dehydrocholesterol.

Biotransformation
By means of a specific transport protein vitamin D reaches the liver where it is metabolized by a microsomal hydroxylase to 25-hydroxy-cholecalciferol.

Elimination
The excretion of vitamin D and its metabolites is carried out biliary/faecal.

Vitamin D is stored in fatty tissue and has therefore a long biological half-life. After high vitamin D doses the 25-hydroxyvitamin D concentrations in serum can be increased for months. Hypercalcemia caused by overdose can persist for weeks (see section 4.9).

5.3 Preclinical safety data

There are no further special toxicological risks to humans apart from these listed under the sections 4.6 and 4.9.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate; sodium hydroxide; sorbitol, liquid 70% (crystallizing); polysorbate 80; triglycerides, medium-chain; water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

In D_3-Vicotrat the fat-soluble vitamin D_3 is dispersed with solubilizers in water. Hereby an opalescent "solution" develops, appearing more or less turbid in incident light (Tyndall effect). The turbidity of the solution may be influenced by concentration and temperature and the solution may tend to emulsify. However, an appearing turbidity does not influence the effectiveness of the preparation.

6.4 Special precautions for storage

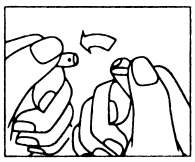
Do not store above 25 °C.

After opening of the ampoules any leftover content must be discarded.

6.5 Nature and contents of container

5 ampoules with 1 ml of solution for injection each.

6.6 Special precautions for disposal and other handling



CBR ampoule

To open, break off the neck at the break ring with a downward movement.

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

6813051.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 February 1999
Date of latest renewal: 06 August 2009

10. DATE OF REVISION OF THE TEXT

June 2021

11. PRESCRIPTION STATE

By prescription only