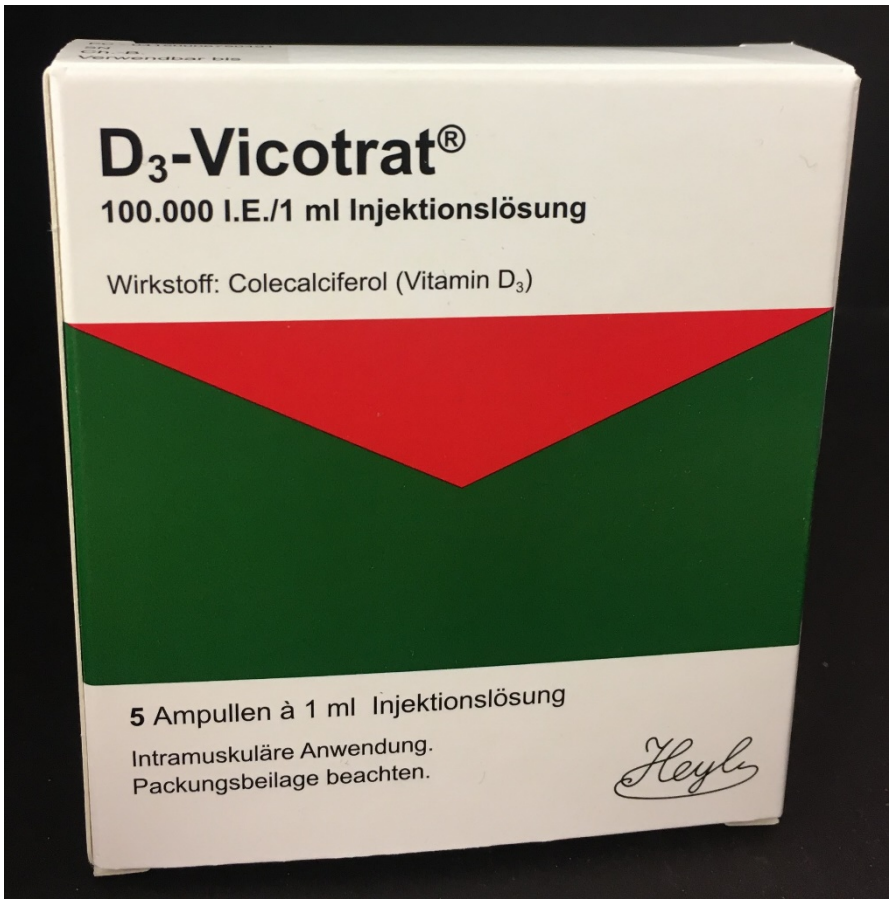
D_3-Vicotrat®



Content: **Vitamin D_3**

D_3-Vicotrat® at a glance

SmPC D_3-Vicotrat®

D_3-Victotrat

3rd edition

February 2021

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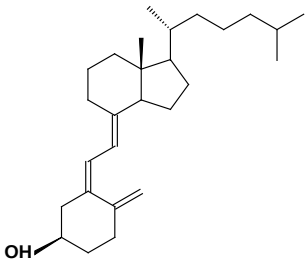
USt-IdNr.: DE 136648757, Managing director: Dr. Eduard Heyl, Alexander Heyl

Vitamin D_3

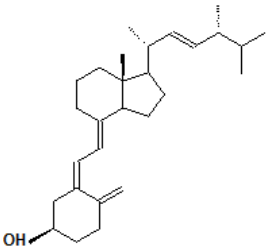
Introduction:

Vitamin D is not really a vitamin, since it is not an essential dietary factor. It is rather a prohormone produced photochemically in the skin. Vitamin D is a fat-soluble steroid hormone that is obtained by sun exposure, diet, or supplements and is crucial for human health. Vitamin D insufficiency appears to be a common health issue all over the world. Vitamin D_3 has a wide range of physiological functions in the body which are mediated by its metabolite 1α, 25-hydroxyvitamin D_3 (1, 25 $(OH)_2$ D_3) that regulates calcium and phosphorus metabolism in concert with parathyroid hormone. There is growing evidence showing the importance of adequate vitamin D supply for preserving health. Vitamin D is globally known for its importance in bone mineral metabolic health promotion and was traditionally known as the “sunshine” vitamin because of its antirachitic properties. In recent years, vitamin D has been studied for its potential extraskeletal role in the prevention of cancers, cardiovascular diseases, autoimmune diseases, and other chronic conditions. Hypovitaminosis D has been associated with rickets, osteomalacia, osteoporosis and fractures, falls in the elderly, diabetes, multiple sclerosis, and many other conditions. In infants and children, hypovitaminosis D has been associated with rickets, impaired growth, developmental delays, lethargy, hypocalcemic seizures, respiratory infections, type 1 diabetes and cardiomyopathy. Thus, its optimal presence in the body is of exceptional significance for health of children, as well as adults and older persons. Cholecalciferol is listed in the current “WHO Model List of Essential Medicines” 2015 for adults and children.

Vitamin D_2 or vitamin D_3:



Vitamin D_3 (Cholecalciferol)
$C_{27}H_{44}O$



Vitamin D_2 (Ergocalciferol)
$C_{28}H_{44}O$

Vitamin D is classified as a secosteroid and refers to both cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Cholecalciferol is produced in the skin of humans and is the form of vitamin D found in oily fish and egg yolk. Ergocalciferol is obtained by irradiation of plants, e.g. when ultraviolet (UV) light irradiates the fungal steroid, ergosterol. A meta-analysis indicates that vitamin D_3 is more efficacious at raising serum 25(OH)D concentrations than vitamin D_2, and thus vitamin D_3 could potentially become the preferred choice for supplementation. A trial conducted in 2012 comparing large doses of vitamin D_2 versus vitamin D_3 does suggest that vitamin D_3 supplemen-

tation results in a higher increase of 25-hydroxyvitamin D [25(OH)D] over time[1]. A randomized controlled trial compared the effect of 1000 IU vitamin D_3 and D_2 daily, revealing a significantly lower 25(OH)D mean serum level in the D_2 supplemented group after 25 weeks[2]. This effect was confirmed in a recent trial comparing 600 IU per day vitamin D3 with vitamin D2 for 3 months[3].

The intake of vitamin D is ususally expressed in International Units (IU) or in micrograms (µg). In 1950 the World Health Organization (WHO) defined one IU as the activity produced by 0.025 µg of crystalline vitamin D_3.

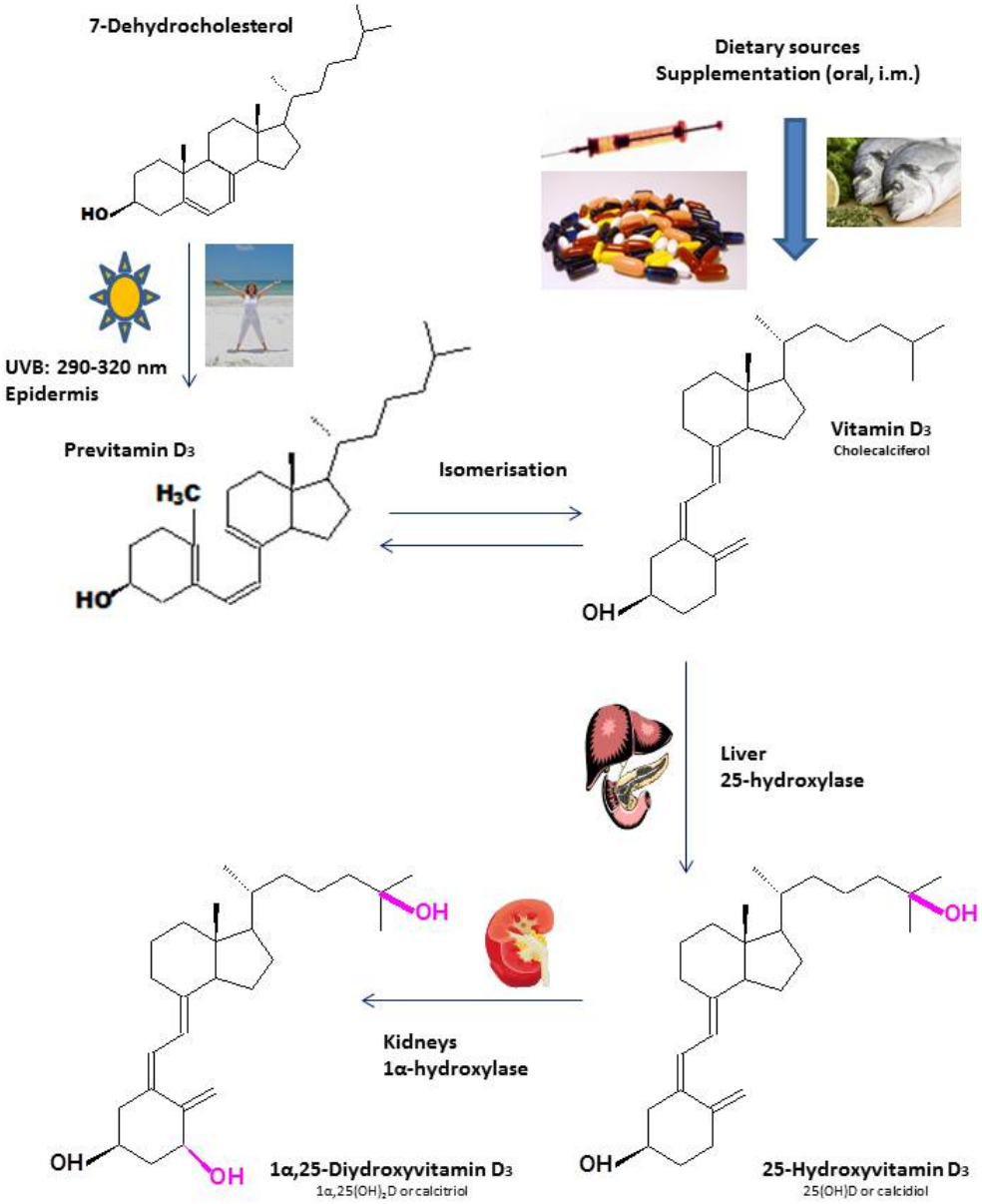
Oral or i.m. application of vitamin D_3:

If additional endogenous synthesis of vitamin D is not feasible for any reason vitamin D supplementation is an important strategy for preventing low levels of serum 25OHD and improving bone health and consequent associated health risks, especially in people at risk of deficiency. Additionally, vitamin D supplementation may improve muscle function in adolescents and adults over 50 years with a mean serum 25(OH)D concentration of less than 30 nmol/L[4]. The aim of treatment should be achieving a serum level of over 75 nmol/L.
Both oral and intramuscular (i.m.) preparations of vitamin D are effective, safe, and practical in treating hypovitaminosis D[5].
Although the oral route may be more convenient and physiological, the i.m. route may be useful in certain situations, specifically for intermittent high-dose regimens and for patients with malabsorption. Individuals with short bowel syndrome may require intermittent i.m. dosing to achieve acceptable vitamin D status. Similarly, concordance with oral medication in elderly individuals in care homes may be variable, and an intermittent i.m. administration has proved effective in long-term prevention of deficiency[6]. For severe vitamin D deficiency the intramuscular administration form of cholecalciferol 100,000 IU (megadose therapy) may be more suitable to replenish stores more quickly and effectively[7]. If compliance of patients is poor or where oral therapy is not tolerated, i.m. injection of cholecalciferol allows safe and inexpensive patient care. Patients no longer have to remember to take their daily pills. One injection every three months fits the requirement of vitamin D. Intramuscular vitamin D significantly improves 25(OH)D levels compared to no treatment and may combat non-compliance with oral medication[8].

Metabolism of vitamin D_3:

During exposure to sunlight 7-dehydrocholesterol absorbs ultraviolet radiation resulting in cutaneous production of previtamin D_3 in the epidermis. Exposure of approximately 25% of body surface, 2-3 times per week to a quarter of the miminal erythema dose in spring to fall is equivalent to an oral dose of 25 µg vitamin D[9,10]. However, the production of vitamin D in the skin decreases with age and with darker skin pigmentation. Then, in the basal cells of the epidermis, the previtamin D_3 is isomerized to vitamin D_3. Bound to vitamin D-binding protein in blood, it is transported to the liver where it is hydroxylated by a cytochrome P450 enzyme into 25-hydroxyvitamin D [25(OH)D, or calcidiol], the major circulating form of vitamin D. The

concentration of 25(OH)D in the serum reflects total body stores of vitamin D, and is used to assess vitamin D status. In the kidney, 25(OH)D is hydroxylated to produce the biologically active hormone 1α,25-dihydroxyvitamin D (1α,25(OH)$_2$D), also known as calcitriol. It exerts its effect by binding to the vitamin D receptors (VDRs) belonging to the steroid/thyroid hormone receptor family, which are distributed in more than 39 different tissues across the body including thyroid[<11>]. An increasing amount of evidence has established that this metabolite possesses immunoregulatory properties[<12>].



Vitamin D status: There is a high prevalence of vitamin D insufficiency worldwide, both in the developed as well as in the developing world. The dose needed to maintain acceptable serum levels of vitamin D seems to be greater than currently recommended daily intake, at least during winter time. Serum 25(OH)D concentration reflects exogenous intake as well as endogenous synthesis and is the best marker of bodily vitamin D status due to its long half-life in the circulation. Serum concentrations are expressed as nanomoles per litre (nmol/L) or nanograms per millilitre (ng/mL). 2.5 nmol/L is equivalent to 1 ng/ml. Serum 25(OH)D concentration is recommended to not fall below 25 nmol/L at any time of the year[4]. Moreover, concentrations ≥ 50 nmol/L shall ensure an adequate vitamin D status for 99 % of the population. Serum 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the active vitamin D hormone, should not be measured as it has a short circulating half-life and does not reflect body vitamin D status[6]. Its measurement is not indicated in routine clinical practice.

Status	25(OH)D [ng/mL]	25(OH)D [nmol/L]
Severe deficiency	< 10	< 25
Deficiency	10-19	24-49
Insufficiency	20-29	50-74
Optimal range	30-50	75-125
Overdosage, possible adverse effects	>100	>250

Vitamin D status and serum 25(OH)D levels[13,14,15,16]

Kinetic of vitamin D: The oral and i.m. routes clearly display different pharmacokinetics. Whereas the oral route leads to an increase in serum 25(OH)D levels within 3 days, the i.m. route leads to a sequestration in the muscle and fat with gradual release into the vascular system. The serum 25(OH)D levels do not increase rapidly within the first week. There was a gradual increase in serum 25(OH)D levels from the first week to 2 months[6]. Cholecalciferol (but not 25(OH)D) crosses into breast-milk. Circulating 25(OH)D has the longest half-life (3–6 weeks) of vitamin D metabolites[17].

Safety of vitamin D: Prolonged sunlight exposure does not lead to excess production of cutaneous vitamin D as a regulation mechanism exists to destroy excess pre-vitamin D_3 in the skin. However, high doses of vitamin D supplements can be toxic and can result in hypercalcaemia with demineralisation of bone, soft tissue calcification and renal damage. The symptoms and findings associated with vitamin D intoxication are closely related to serum calcium concentration and duration of hyper-calcemia. This is likely to occur only if high dose formulations are taken over a prolonged period of time. The maximum safe bolus and regular daily doses of calciferol remain uncertain. Selecting hypercalcaemia as an indicator for toxicity the European Food Safety

Authority considered the tolerable upper level (TUL) of vitamin D intake at 4000 IU/day for adults and children aged 11-17 years appropriate. The TUL for children aged 1-10 years was set at 2000 IU/day and for infants at 1000 IU/day [18]. However, cholecalciferol has a high therapeutic index, meaning that large doses can be administered with little chance of toxicity, particularly to individuals with biochemically documented vitamin D deficiency. Owing to the high therapeutic index, there are multiple effective dosing regimens for the treatment of vitamin D deficiency. Care has to be taken with regard to calcium intake, as a too high dose of calcium may increase cardiovascular disease risk[17]. Vitamin D is relatively safe, but not completely safe, it is necessary to pay attention to adverse events like hypercalciuria and hypercalcaemia and to check 25(OH)D concentration in all the patients taking active vitamin D drugs, especially at high dosage regimens. “Evidence from clinical trials shows, with a wide margin of confidence, that a prolonged intake of 10,000 IU/d of vitamin D poses no risk of adverse effects for adults, even if this is added to a rather high physiologic background level of vitamin D”[19]. Other authors note that 25(OH)D concentrations up to 250 nmol/L are safe and still leave a broad margin for error because values significantly higher than this value have never been associated with toxicity[20].

Risk of Vitamin D deficiency

The major natural source of vitamin D is sunlight, with a small amount (10 – 20 %) coming from the diet. However, sun exposure for vitamin D production has to be balanced against adverse biological effects of UV exposure including sunburn, photoageing or even skin cancer. Vitamin D deficiency is defined as 25-hydroxyvitamin D levels < 20 ng/ml (50 nmol/L). Using these levels, one billion people worldwide have vitamin D deficiency. Certain individuals are at increased risk of vitamin D deficiency:

- people with pigmented skin
- those who lack exposure to sunlight, even all ages living an “indoor” lifestyle
- people who wear skin-concealing garments or use sunscreen excessively
- infants who are exclusively breast fed
- women who have multiple pregnancies with short intervals
- elderly, obese or institutionalised people
- vegetarians
- people who suffer from malabsorption, short bowel, liver or renal disease
- individuals who take certain pharmacological agents[21].

Conclusion:

Vitamin D insufficiency is a very common, underdiagnosed problem affecting all age groups, but especially the older population. It is associated with skeletal and nonskeletal conditions which cause significant morbidity and mortality. It is both treatable and preventable and innovative approaches to its management such as intramuscular replacement and supplementation are both practically feasible and promising[22].

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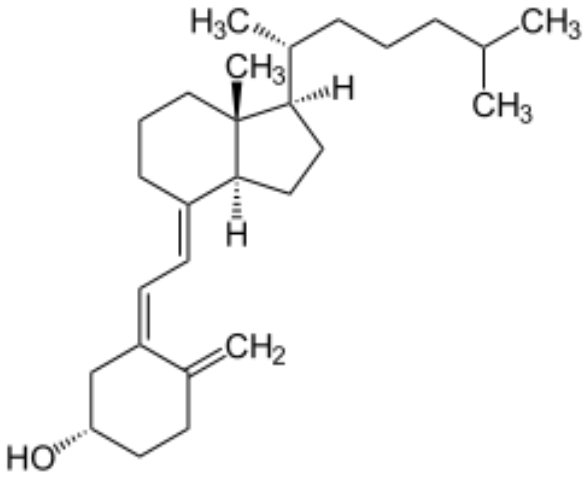
D_3-Vicotrat® at a glance

Active substance:	Cholecalciferol (Vitamin D_3) PH. EUR $C_{27}H_{44}O$
Chemical name:	(5Z,7E,3S)-9,10-Secocholesta-5,7,10(19)-trien-3-ol (IUPAC)
CAS-No.:	67-97-0



ATC Code (DIMDI):	A11CC05 (Colecalciferol)
PZN product code:	0679049
Marketing authorization number:	6813051.00.00 (BfArM)
Date of marketing authorisation:	February 02, 1999
Date of last renewal of marketing authorization:	August 08, 2009 This renewal of the approval was granted without any temporary restrictions
Date of the last PSUR:	May 25, 2012
MA holder (MAH):	HEYL Chem.-pharm. Fabrik GmbH & Co. KG Kurfürstendamm 178/179 10707 Berlin

World-wide marketing authorisation status :

D_3-Vicotrat® is the only approved vitamin D_3 preparation for intramuscular application in Germany. It is marketed for more than 40 years and was registered for the BGA on December 06, 1968 under the number D 1194. In the course of authorisation renewal, it was approved under marketing authorisation no. 6813051.00.00 on February 02, 1999. The last renewal of the approval without any temporary restrictions was granted on August 08, 2009. The preparation is currently also approved in South Korea, where BL&H Co. Ltd. is the marketing authorization holder.

Indication:

D_3-Vicotrat® is used for the prophylaxis of vitamin D deficiency symptoms due to malabsorption, caused by chronic intestinal diseases, scarred alteration of the liver tissue (biliary hepatocirrhosis), extended stomach or intestines resections, if an oral therapy is impossible or ineffective.

Composition:

D_3-Vicotrat® is water based, not an oil based product. Therefore the product may be administered to patients who are allergic to oils. In D_3-Vicotrat® the fat-soluble cholecalciferol is dispersed with solubilizers in water. Hereby an opalescent "solution" forms, appearing more or less turbid in incident light (Tyndall effect). The turbidity of the solution may be influenced by concentration and temperature.

Ampoules with 1 ml of injection solution for intramuscular injection contain 2.5 mg cholecalciferol corresponding to 100,000 IU of vitamin D_3. The origin of active ingredient is wool grease. Therefore the product is suitable for vegetarians but not for vegans.

The other components of D_3-Vicotrat® are: Medium-chained triglycerides, polysorbate 80, sodium dihydrogenphosphate 2 H_2O, sodium hydroxide, sorbitol solution 70 % (crystallizing) and water for injections.

Dosage:

The immediate aim of treatment is to replenish vitamin D stores. The recommended dose of D_3-Vicotrat® is 100,000 IU every 3 months. This corresponds to a dose of 400,000 IU per year or 1,100 IU per day.

Side effects:

The side effects of vitamin D result as a consequence of the hypercalcemia at overdose.

HEYL did not receive any spontaneous reports of suspected unexpected adverse reactions from health-care professionals or patients during the last years. Also no case reports of overdose of D_3-Vicotrat® became known. A multiple of our recommended dose is often tolerated without complications mentioned in the literature. Intoxications like hypercalcemia appear mainly in case of very high doses. This often results from application errors which lead to a drastic overdose. Since D_3-Vicotrat® is an Rx-preparation and has to be administered by a physician, an excessive intake overdose can be avoided generally.

SmPC 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 solution for injection contains:
2.5 mg cholecalciferol (vitamin D3) 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 re-sections, 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

D3-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.

D3-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 administered, 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 a medical supervision. In such cases the calcium levels in serum and urine must be monitored.

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

D_3-Vicotrat should not be administered to patients who suffer from the rare hereditary fructose intolerance.

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 plasma 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 plasma and urine should be monitored.

Only in exceptional cases and under serum calcium controls D3-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 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, nephroncalcinosis, extraosseous calcifications). In individual cases fatal 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 relatively 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, azotemia, polydipsia and polyuria, finally as exsiccosis. Typical laboratory test results are hypercalcemia, hypercalciuria as well as increased serum levels of 25-hydroxycalciferol.

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, azotemia, 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 of 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 D_2) 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 through

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 month 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 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/fecal.

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 injections.

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

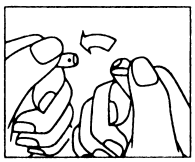
Do not store above 25°C.

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



OPC ampoule

To open, turn so that the point faces upward and break off the neck 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 THE 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

April 2018

11 PRESCRIPTION STATE

By prescription only