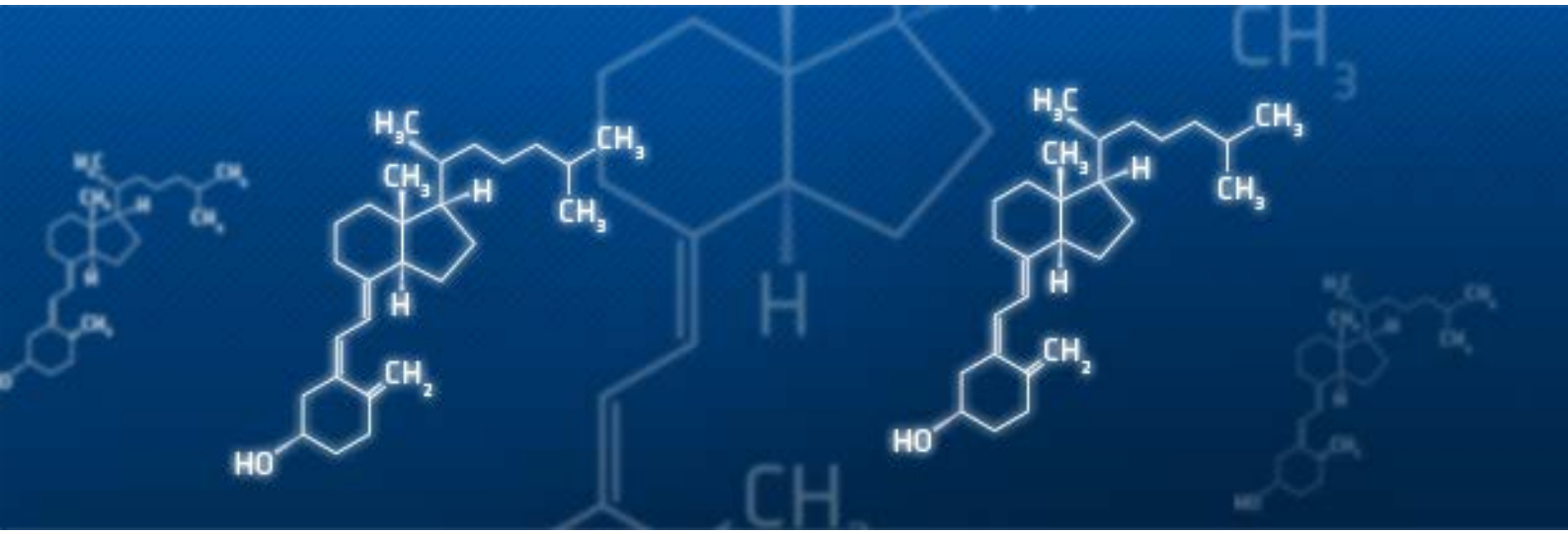
D_3-Vicotrat®

of

Heyl



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D_3-VICOTRAT® OF HEYL

(Product information for healthcare professionals)

Edition 4
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Marketing Authorization Holder:

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REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorization 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.

Contents

Vitamin D

INTRODUCTION

Vitamin D_3 does not correspond to the classical definition of a vitamin since it is not an essential dietary factor. It is rather a prohormone produced photochemically in the skin of many vertebrates including humans. Its existence and its importance for the development of the skeleton was discovered about one hundred years ago (1). Vitamin D_3 is a fat-soluble steroid hormone that is obtained by sun exposure, diet, or supplements. Apart from skeletal targets, it exerts also a crucial role for human health in general. Vitamin D_3 has a wide range of physiological functions in the body which are mediated by its metabolite 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) 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 has already been known for decades 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. Vitamin D insufficiency has become a common health issue all over the world. 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. Supplementary use of vitamin D in infants to prevent rickets is well-established. Thus, its optimal presence in the body is of exceptional significance for health of children, as well as adults and elderly people. Cholecalciferol is listed in the current "WHO Model List of Essential Medicines" 2019 (2) for adults and for children. The intake of vitamin D is usually 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.

VITAMIN D_2 OR VITAMIN D_3

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. Ergocalciferol differs from cholecalciferol for a methyl group in C24 and a double bound in C22-C23 (3). 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 supplementation results in a higher increase of 25-hydroxyvitamin D [25(OH)D] over time (4). 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 (5). This effect was confirmed in a trial comparing 600 IU per day vitamin D_3 with vitamin D_2 for 3 months (6). Bode et al (7) recommend the use of vitamin D_3 over vitamin D_2 for any routine supplementation in elderly, because benefit in decreasing mortality has only been observed with this form.

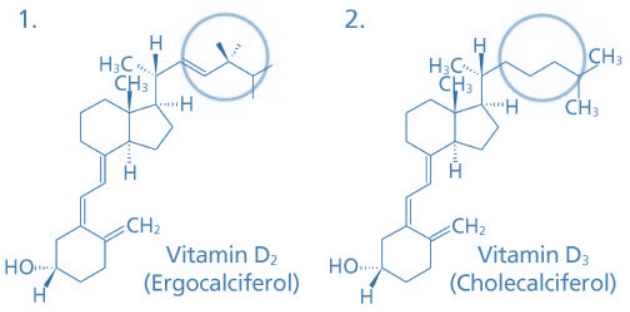


Figure 1: Structures of vitamin D2 and vitamin D3 (35)

PHYSIOLOGY

The major sources of vitamin D are the cutaneous synthesis upon sunlight exposure (about 80%) and, to a minor extent, intake of food (about 20%) (8).

In the skin, vitamin D_3 is produced from 7-dehydrocholesterol, an intermediate in cholesterol synthesis. During exposure to sunlight 7-dehydrocholesterol absorbs ultraviolet-B light (range of 290-315 nm) resulting in cutaneous production of previtamin D_3 in the epidermis. Then, in the basal cells of the epidermis, the previtamin D_3 is isomerized to vitamin D_3 (cholecalciferol). Alternatively, vitamin D_3 is absorbed in the small intestine during intake of food or supplements and is released via the lymph. Bound to vitamin D-binding protein in blood, vitamin D_3 from the skin or oral ingestion is mainly transported to the liver where it is hydroxylated into 25-hydroxyvitamin D [25(OH)D, or calcidiol], the major circulating form. Several enzymes have 25-hydroxylase activity, but CYP2R1 is the most important. Principally in the kidney, 25(OH)D is further hydroxylated by the enzyme CYP27B1 to produce the biologically active hormone 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), also known as calcitriol (9; 10).

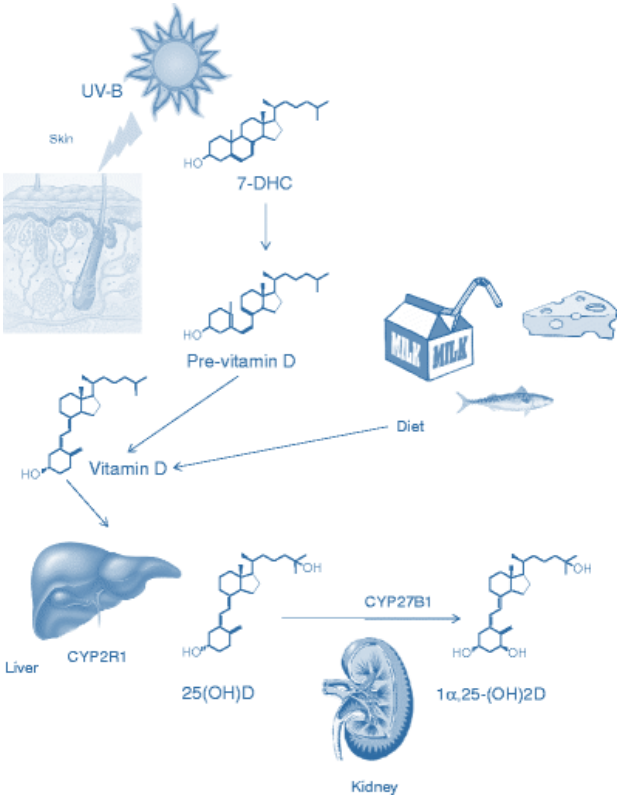


Figure 2: Metabolism of vitamin D (32)

More than 50 metabolites of vitamin D have been described (10). Circulating 25(OH)D has the longest half-life of 15 to 25 days of vitamin D metabolites. The long-term storage of vitamin D is in the adipose tissue (11). The best-known catabolic enzyme is CYP24A1, which converted 25(OH)D and $1,25(OH)_2D$ to an inactive form, calcitic acid, which is eliminated in the bile (10).

The active form of vitamin D ($1,25(OH)_2D$; calcitriol) exerts its effect by binding to the vitamin D receptors (VDRs) belonging to the steroid/thyroid hormone receptor family, which are widely distributed across the body. The classical role of $1,25(OH)_2D$ is in calcium metabolism and bone homeostasis. It is involved in the regulation of intestinal calcium absorption, renal calcium and phosphate reabsorption and mobilization of calcium and phosphate from bone together with parathyroid hormone and fibroblast growth factor 23 (8; 10).

Additionally, vitamin D has been reported to have pleiotropic effects on several districts, particularly the immune system and the cardiovascular system, but also on cancer (10; 9).

VITAMIN D STATUS AND VITAMIN D INSUFFICIENCY

Serum 25(OH)D concentration is the best marker of bodily vitamin D status due to its long half-life in the blood circulation and reflects exogenous intake as well as endogenous synthesis. 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 (12). Moreover, concentrations ≥ 50 nmol/L shall ensure an adequate vitamin D status for 99 % of the population. Serum $1,25(OH)_2D$, the active vitamin D hormone, should not be measured in routine clinical practice as an indicator as it has a short circulating half-life and does not reflect body vitamin D status (13).

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

Figure 3: Vitamin D status and serum 25(OH)D levels (14; 15; 16; 17)

As mentioned already earlier, the major natural source of vitamin D is sunlight, only a small amount (10 – 20 %) coming from the diet. Thus, the major cause for deficiency is a lack of sunlight. 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. Exposure of approximately 25% of body surface, 2-3 times per week to a quarter of the minimal erythema dose in spring to fall is equivalent to an oral dose of 1000 IU vitamin D (18; 19). However, the production of vitamin D in the skin is dependent on many factors like age, geographical location and latitude, genetic polymorphisms, skin pigmentation, clothing and body surface area exposed, decreases with age and with darker skin pigmentation. Vitamin D deficiency is defined as 25(OH)D levels < 20 ng/ml (50 nmol/L). Using these levels, one billion people worldwide have vitamin D deficiency, most common in the Middle East, India, Africa, and South America (20). Certain individuals are at increased risk of vitamin D deficiency:

- people with naturally dark skin tone
- 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 institutionalized people
- vegans and vegetarians
- people who suffer from malabsorption, short bowel, liver or renal disease
- individuals who take certain pharmacological agents (21).

TREATMENT OPTIONS

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 25(OH)D and improving bone health and consequent associated health risks, especially in people at risk of deficiency. The dose needed to maintain acceptable serum levels of vitamin D seems to be greater than currently recommended daily intake of 600 IU for adults (22), at least during winter time.

There are multiple effective dosing regimes for the treatment of vitamin D deficiency. In general, a distinction can be made between regular, low-dose treatment and intermittent, high-dose treatment. This intermittent high-dose therapy (known as “stoss” therapy in parts of continental Europe) can be an attractive option as poor patient compliance with therapy may be a problem, especially in asymptomatic individuals (23).

Both oral and intramuscular (i.m.) preparations of vitamin D are effective and safe in treating hypovitaminosis D (24; 25; 26). 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 or after bariatric surgery may require intermittent i.m. dosing to achieve acceptable vitamin D status (23; 27). 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 (23).

The two routes have different pharmacokinetics. After i.m. injection of 100 000 IU vitamin D, serum 25(OH)D concentrations increased significantly in the first 7 days and peaked after 4 weeks, after which it decreased in the following 4 weeks (28). In comparison, the increase in serum 25(OH)D levels were more rapid but also more transient after oral administration of vitamin D. The sustained levels of serum 25(OH)D concentrations can be explained by the vitamin D fat tissue storage capacity with a slow and gradual release of i.m. administered cholecalciferol. However, the mean 25(OH)D concentration increase was comparable after i.m. and oral treatment (24).

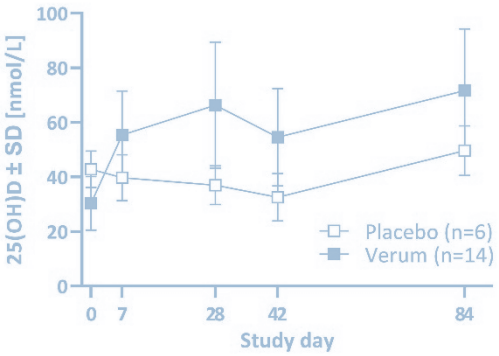


Figure 4: Course of serum 25(OH)D concentrations in vitamin D-deficient subjects after a single dose of 100 000 IU cholecalciferol i.m. (D_3-Vicotrat; verum) or placebo (28)

VITAMIN D TOXICITY

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 hypercalcemia with demineralization of bone, soft tissue calcification and renal damage.

The symptoms and findings associated with vitamin D toxicity (VDT) are closely related to serum calcium concentration and duration of hypercalcemia. Most often noted clinical symptoms include neuropsychiatric manifestations, such as difficulty in concentration, confusion, apathy, drowsiness, and in extreme cases, a stupor and coma. The gastrointestinal symptoms of VDT include recurrent vomiting, abdominal pain, polydipsia, anorexia, constipation, peptic ulcers, and pancreatitis. The cardiovascular manifestations of VDT include hypertension, shortened QT interval, and bradyarrhythmia with first-degree heart block on the electrocardiogram. The renal symptoms include hypercalciuria as the earliest sign, polyuria, polydipsia, dehydration, nephrocalcinosis, and renal failure. Other symptoms of VDT caused by hypercalcemia include band keratopathy, hearing loss, and painful periarticular calcinosis.

VDT resulting in hypercalcemia is rare. In healthy individuals, VDT is usually caused by prolonged use of vitamin D mega doses. The unintentional overdosing due to use of pharmaceutical products is the most frequent cause of exogenous VDT. An overview of VDT cases caused by vitamin D formulation or administration errors that resulted in excessive dosing confirmed that intoxication is extremely rare (29).

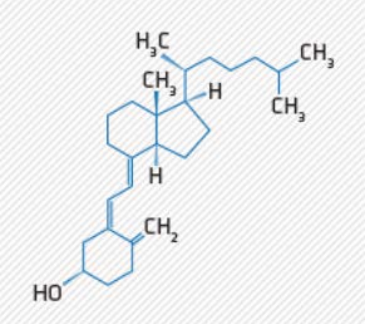
The maximum safe bolus and regular daily doses of calciferol remain uncertain. Selecting hypercalcemia as an indicator for toxicity the European Food Safety Authority considered the tolerable upper level (TUL) of vitamin D intake at 4000 IU/day for adults and children aged 11-17 years appropriate. The TUL for children aged 1-10 years was set at 2000 IU/day (30), for infants aged 6-12 months at 1400 IU/day and for infants aged up to 6 months 1000 IU/day (31).

In some clinical conditions, endogenous VDT is also an important clinical issue. Endogenous etiologies may develop from ectopic production of $1,25(OH)_2D$ in granulomatous diseases, such as sarcoidosis and tuberculosis, or in lymphoma. Researchers have proposed many processes to account for VDT, including the inhibited activity of 24-hydroxylase or elevated activity of 1α-hydroxylase, both leading to increased concentration of the active vitamin D metabolite, or the increased number of VDRs.

Vitamin D toxicity due to vitamin D overdosing is diagnosed by markedly elevated 25(OH)D concentrations (> 150 ng/mL; > 375 nmol/L) accompanied by severe hypercalcemia and hypercalciuria and by very low or undetectable parathyroid hormone activity (29).

Vitamin D is relatively safe, but it is necessary to pay attention to adverse events like hypercalciuria and hypercalcemia and to check 25(OH)D concentration in all the patients taking active vitamin D drugs, especially at high dosage regimens.

Overview: D_3-Vicotrat®

ACTIVE SUBSTANCE	Cholecalciferol (Vitamin D_3) 
PHARMACEUTICAL FORM AND ADMINISTRATION	Solution for injection for intramuscular use 
PHARMACEUTICAL STRENGTH	2.5 mg corresponding to 100 000 IU
ATC CODE	A11CC05
THERAPEUTIC INDICATION	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.
PRESCRIPTION STATE	By prescription only
NTIN	04150006790491
PACK SIZE	5 ampoules à 1 ml

Information on D_3-Vicotrat®

GENERAL

D_3-Vicotrat is the only pharmaceutical form of vitamin D_3 approved for intramuscular application in Germany. It is marketed for more than 40 years.

The medicinal product is currently also approved in South Korea, where BL&H Co. Ltd. is the marketing authorization holder.

COMPOSITION

Solution for injection for intramuscular use.

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

Other ingredients: Sodium dihydrogen phosphate dihydrate; sodium hydroxide; sorbitol, liquid 70% (crystallizing); polysorbate 80; medium-chained triglycerides; water for injections.

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.

THERAPEUTIC INDICATION

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.

DOSAGE

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 hemolysis depending on the applied dosage.

Pediatric Population

There is no expert knowledge with children.

CONTRAINDICATION

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

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 considered. 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Phenytoin 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.

FERTILITY, 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.

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.

ADVERSE DRUG REACTIONS

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.

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 diarrhea, later 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-hydroxycholecalciferol.

Treatment of overdose

In case of an overdose, measures to treat 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 calcitonin 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. Hemodialysis (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.

PHARMACEUTICAL PARTICULARS

INCOMPATIBILITIES

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

SHELF LIFE

The shelf-life is 3 years.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Do not store above 25°C.

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

MARKETING AUTHORIZATION

Marketing authorization number in Germany: 6813051.00.00
Date of first authorization: 02 February 1999

By prescription only.

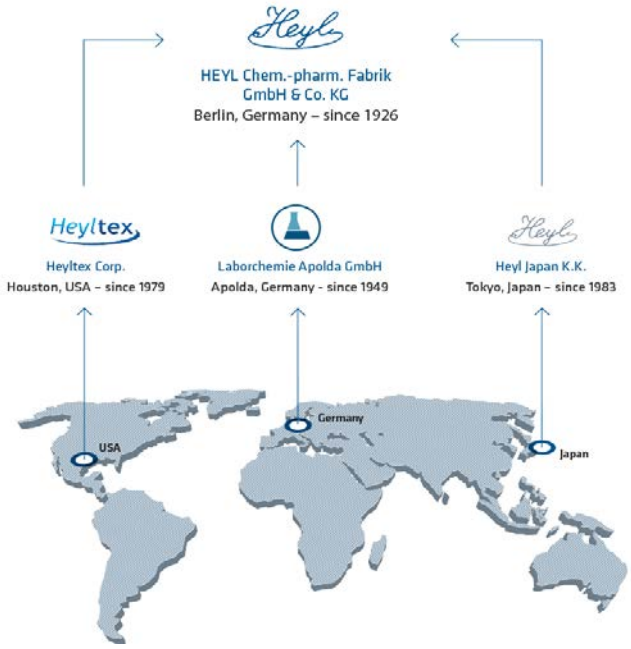
Company Profile

HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG is a non-corporate, independent family-owned company with headquarters in Berlin, the most vibrant metropolitan area in Germany today. The company was founded nearly one hundred years ago, in 1926. In those days, its focus was the extraction and processing of cod-liver oil according to its own patented methods in addition to the manufacture of vitamins, which were novel products back then.

Today, HEYL is a company focused on specialty fields. As a niche specialist we concentrate on products that are too small for big corporations and too large for smaller businesses. Following this strategy, HEYL has developed a number of antidotes in collaboration with various national and international research institutes and universities over the course of the last 35 years. These antidotes are highly effective drugs used to treat poisoning with thallium, arsenic or heavy metals (mercury and lead) and contamination with radioactive isotopes such as radioactive cesium or plutonium. Purchase orders from all over the world attest to the medical importance of these drugs.

In collaboration with its international subsidiaries, HEYL has made drug approval and marketing as well as the distribution of pharmaceuticals and special chemicals a focus of business. To achieve the goal of establishing a presence in important foreign markets such as the USA and Japan, the Heyltex Corporation was founded in Texas/USA in 1979 and the Heyl Japan Co. Ltd. in Tokyo/Japan in 1983.

Since its establishment, HEYL has strived for maintaining independent manufacture of key active substances for its pharmaceutical products. To improve its production capabilities in the field of chemical synthesis, HEYL took over the privatized Laborchemie Apolda GmbH in Thuringia and made it a 100 % subsidiary in 1993.



In Berlin, its German and international headquarters, HEYL brings together medical-scientific know-how and experience with its knowledge of regulatory affairs and many years of competence in marketing.

Our management and staff make every effort to promote the competitiveness of our location in Germany through excellence and price discipline.

HEYL will continue providing pharmaceutical products with the highest level of therapeutic efficacy and safety to medical experts and patients needing them. We guarantee excellent service by ensuring high-quality products, expert services and punctual delivery.

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Information is based on the current summary of product characteristics of D_3-Vicotrat®.

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