SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Vigalex Max, 100 micrograms (4000 IU), tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains cholecalciferol 40 mg, powder form, equivalent to 0.1 mg of cholecalciferol (Vitamin D_3).

Excipients with known effect: Each tablet contains sucrose 7 mg.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablets, 10 mm ± 0.3 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of vitamin D deficiency and conditions resulting from vitamin D deficiency (e.g. osteomalacia, osteoporosis) in obese adults (body mass index, BMI ≥ 30 kg/m^2)

4.2 Posology and method of administration

Without medical supervision, do not use other medications or dietary supplements as well as any other types of food containing vitamin D (cholecalciferol), calcitriol and other metabolites and analogues of vitamin D.

The medicinal product should not be used without medical supervision for a long time (more than 3 months) or in doses higher than recommended.

Prophylaxis of vitamin D deficiency and conditions resulting from vitamin D deficiency in obese adults
The usual recommended dose is 4000 IU/day, from October to April or throughout the year in case if effective skin synthesis of vitamin D is not ensured during the summer months (see section 4.4).

Patients with renal impairment
Vigalex Max should not be used in patients with renal impairment without medical supervision (see section 4.4).

Patients with hepatic impairment
No dose adjustment is necessary.

Children and adolescents
Due to a dose of cholecalciferol equal 4000 IU the use of Vigalex Max is contraindicated in children and adolescents under 18 years of age.

Method of administration
The tablet should be swallowed with sufficient amount of liquid.

4.3 Contraindications

- Hypersensitivity to the active substance (cholecalciferol) or to any of the excipients listed in section 6.1;
- Hypercalcaemia and/or hypercalciuria;
- Nephrolithiasis and/or severe renal impairment;
- Pseudohypoparathyroidism (vitamin D requirements may be diminished due to periods of normal sensitivity to this vitamin, leading to overdose). In such case more manageable vitamin D derivatives are available;
- Children and adolescents under 18 years of age.

4.4 Special warnings and precautions for use

The total dose of vitamin D in patients is made up of the vitamin D content taken with other medicinal products and with vitamin D-rich food consumed. And the vitamin is produced by the body through of its exposure to sunlight.
In Poland, sufficient exposure to sunlight is possible only in the period from May to September and requires at least 15 minutes of exposure to sun a day from 10:00 a.m. and 3 p.m., with naked forearms and lower legs, without the use of sunscreen.

Additional doses of vitamin D or calcium can be used only under medical supervision. In such cases the serum and urine calcium levels should be monitored.

In patients with sarcoidosis Vigalex Max should only be administered with extreme caution due to the risk of the excessive metabolism of vitamin D to active metabolites. In these patients serum and urine calcium levels should be monitored.

In patients with renal impairment treated with Vigalex Max the metabolism of calcium and phosphate should be monitored.

Obese patients (adults - BMI $\geq$ 30 kg/m^2) require twice the dose of vitamin D than recommended for their normal weight peers.

In the case of long-term use of cholecalciferol, especially when a daily dose exceeding 1000 IU of vitamin D, the calcium levels in the serum and urine and renal function should be monitored by the measurement of creatinine concentration. This is particularly important in the case of elderly patients and with concomitant treatment with cardiac glycosides or diuretics.

In the case of hypercalcaemia or signs of renal impairment the dose should be reduced or the treatment should be discontinued. Dose reduction or treatment discontinuation is recommended if the daily urinary calcium excretion exceeds 7,5 mmol/24 hours (300 mg/24 hours).

This medicine contains less than 1 mmol (23 mg) sodium per the recommended dose unit, therefore the medicine is considered "sodium-free".

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The use of aluminium-containing antacids with Vigalex Max may lead to an increase of blood aluminium levels, increasing the risk of bone toxicity of aluminium.

Antacids, containing magnesium, taken concomitantly with vitamin D, may increase magnesium concentration in blood.

Phenytoin and barbiturates may reduce the effect of vitamin D. Concentrations of 25-hydroxy-vitamin D may be decreased and metabolism to inactive metabolites may be enhanced.

Thiazide diuretics may lead to hypercalcaemia due to decreased renal calcium excretion. In long-term treatment, serum and urine calcium levels should be monitored.

Concomitant treatment with glucocorticoids may offset the effect of cholecalciferol.

Digitalis (cardiac glycosides): oral administration of vitamin D may increase the effect and toxicity of digitalis.
During treatment with vitamin D the toxicity of cardiac glycosides may be increased as a result of the increased calcium levels (risk of developing arrhythmias). Patients' serum and urine calcium levels should be monitored and periodic ECG examinations performed.

Vitamin D metabolites or analogues (e.g. calcitriol): concomitant treatment with Vigalex Max is recommended only in exceptional cases and under the control of calcium concentration in serum.

Rifampicin and isoniazid: may increase vitamin D metabolism and decrease its effectiveness.

4.6 Fertility, pregnancy and lactation

Pregnancy
Women during the procreation period and planning pregnancy should be guaranteed an adequate supply of vitamin D as in a general adult population, and if possible under the control of the serum 25(OH)D.

Once the pregnancy is confirmed, the supplementation should be carried under the control of serum 25(OH)D in order to maintain the optimal concentration in the range >30–50 ng/mL.

If determination of serum 25(OH)D is not possible, the use of vitamin D at the dose of 2000 IU/day is recommended throughout pregnancy.

Breast-feeding
Vitamin D and its metabolites are excreted in human milk but in small amounts. Thus there was not observed overdose in newborns and infants. Breastfed infants require additional supplementation of vitamin D.

If determination of serum 25(OH)D in patient is not possible, use of vitamin D at the dose of 2000 IU/day is recommended for the entire breastfeeding period.

4.7 Effects on ability to drive and use machines

Vigalex Max has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are ranked using the following convention:
- common (≥1/100 do <1/10);
- uncommon (≥1/1 000 do <1/100);
- rare (≥1/10 000 do <1/1 000);
- very rare (≤1/10 000);
- not known (may not be estimated from the available data.).

System Organ Classes	Frequency	Undesirable effects
Gastrointestinal disorders	Not known	Gastrointestinal disorders such as: constipation, flatulence, nausea, abdominal pain or diarrhoea.
Skin and subcutaneous tissue disorders	Not known	Hypersensitivity reactions such as itching, rash or urticaria.
Metabolism and nutrition disorders	Not known	Hypercalcemia and hypercalciuria in case of long-term treatment with high doses. In isolated cases fatalities have been reported (see 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 via the Pharmacovigilance Department of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products:
Al. Jerozolimskie 181C
02-222 Warsaw
Tel.: + 48 22 49 21 301
Fax: + 48 22 49 21 309
Website: https://smz.ezdrowie.gov.pl
Adverse reactions can also be reported to marketing authorisation holder.

4.9 Overdose

In adults overdose may occur after administration of 20 000 to 60 000 IU of cholecalciferol/day and in children after administration of 2000 do 4000 IU during several months. Long-term intake of vitamin without medical supervision is not recommended.

Symptoms

Long-term overdose of vitamin D may cause hypercalcemia and hypercalciuria.
The use of Vigalex Max in doses significantly exceeding the body's demand for vitamin D for the long-term may cause calcification of parenchymal organs.

Ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) have relatively low therapeutic index. Toxicity threshold of vitamin D is between 40 000 and 100 000 IU/day for 1 to 2 months in adults with normal parathyroid function. Infants and children may react with greater sensitivity to much lower doses. Therefore, vitamin D should not be taken without medical supervision.

Overdose causes increased phosphorus serum and urine levels as well as hypercalcemia syndrome, and consequently to accumulation of calcium in tissues, kidneys (nephrolithiasis, nephrocalcinosis) and in vessels.

Symptoms of overdose are not very specific: nausea, vomiting, initially also diarrhoea followed by constipation, loss of appetite, fatigue, headache, muscle pain, joint pain, muscle weakness, somnolence, azotaemia, polyphagia, polyuria and dehydration. If blood level of calcium is above 13 mg/100 ml, cardiac disorders, renal impairment, psychosis or even coma occur.
Laboratory tests show hypercalcemia, hypercalciuria and increased levels of serum 25-hydroxycalciferol.

Vitamin D poisoning may result in death due to renal or heart failure.

Management

In case of vitamin D_3 overdose its administration should be discontinued and the patient should be hydrated.

In case of chronic vitamin D overdose appropriate measures to increase urinary excretion may be necessary as well as administration of glucocorticoids and calcitonin.

In case of overdose it is necessary to take therapeutic measures to compensate prolonged and in some cases life-threatening hypercalcemia.
Treatment with vitamin D should be discontinued; restoration of normal blood calcium levels after vitamin D poisoning causing hypercalcemia symptoms takes several weeks.

Depending on the severity of hypercalcemia the low-calcium or calcium-free diet, a high fluid intake, forced diuresis with furosemide, glucocorticoids and calcitonin should be used.

In case of normal renal function calcium level may be reduced by infusion of the isotonic solution of NaCl (3 to 6 liters in 24 hours) with furosemide, calcium chelators and glucocorticoids. In some cases edetic acid salt in quantity of 15 mg/kg bw/hour should be applied, calcium level and ECG monitored. In oligonuria haemodialysis is required (calcium-free dialysis).

There is no specific antidote.

The patients undergoing chronic treatment with higher doses of vitamin D should be informed of the symptoms of a potential overdose (nausea, vomiting, diarrhoea followed by constipation, loss of appetite, fatigue, headache, muscle pain, joint pain, muscle weakness, somnolence, azotaemia, polyphagia, polyuria).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vitamin D preparations and its analogues
ATC code: A11CC05

Cholecalciferol (vitamin D_3) is produced in skin upon the exposure to UV radiation and is converted into a biologically active, i.e. 1.25-dihydroxycholecalciferol in two stages: first in the liver (hydroxylation in position 25 to calcifediol), and then in kidneys (hydroxylation in position 1 to calcitriol). Calcifediol and calcitriol, active metabolites of cholecalciferol, regulate transcription and translation process through steroid nuclear receptors in DNA, determine synthesis of proteins responsible for calcium absorption in the body and proteins determining bone mineralization. 1,25-dihydroxycholecalciferol along with parathyroid hormone and calcitonin are mainly responsible for maintaining the calcium and phosphate homeostasis. Cholecalciferol, via the active metabolites, mainly calcitriol, increases calcium and phosphate absorption in gastrointestinal tract, reabsorption of calcium in kidneys and blood calcium and phosphate levels. It inhibits excretion of parathyroid glands hormone, facilitates bone mineralization and prevents calcium loss from the body.
Vitamin D deficiency causes disorders of bone calcification (rickets) or loss of calcium from the bones (osteomalacia).

Basing on its biosynthesis, physiological regulation and mechanism of action, vitamin D_3 is considered a precursor of steroid hormone.

Other information
Fish liver oil (fish oil) and fish meat are foods particularly rich in vitamin D. Minor quantity of this vitamin are also found in meat, egg yolks, milk, dairy products and avocado fruits.

Symptoms of deficiency may appear in premature infants, newborns and infants, who have been exclusively breastfed for more than six months without the addition other calcium-containing foods, and in children on a strict vegetarian diet. Vitamin D deficiency is common in the general population. The causes of the deficiency of this vitamin may include: nutritional deficiencies, insufficient exposure to

UV light, malabsorption from the intestines, poor digestion of nutrients, liver cirrhosis and renal impairment.

5.2 Pharmacokinetic properties

Absorption
Following oral administration cholecalciferol is absorber in the small intestine. Bile and specific proteins determine the absorption process. The absorption of cholecalciferol is increased in presence of fat. Hepatobiliary disorders decrease cholecalciferol absorption.

Distribution
After absorption into the blood, cholecalciferol is transported to the liver, where under the influence of 25-hydroxylase it is converted to calcifediol (25-hydroxycholecalciferol, $25(OH)D_3$). Calcifediol produced in the liver, by the specific transporting proteins (*Vitamin D-binding protein*) present in blood, is transported to the kidneys, where $25(OH)D_3$, under the influence of 1α-hydroxylase, is converted to calcitriol ($1,25(OH)_2D_3$).
Vitamin D_3 and its active metabolites can be stored mainly in liver and in adipose tissue for a long time. In healthy people serum vitamin D_3 is 1.3 nmol/L, and the half-life ($t_{1/2}$) is 19 to 25 hours. Calcifediol half-life is approximately 16 days, and calcitriol is between 3 and 6 hours.

Biotransformation
Vitamin D_3 metabolism leads to formation of pharmacologically active metabolites.
In liver cholecalciferol is hydroxylated in position 25 to $25(OH)D_3$ that is calcifediol.
This process is catalyzed by 25-hydroxylase, and its rate is conditioned by substrate's supply. The activity of this enzyme is lower in premature babies and in patients with hepatic damage. In blood calcifediol is the main circulating metabolite with low activity. The physiological concentration of $25(OH)D_3$ is 10 to 125 nmol/L, and $t_{1/2}$ is from 10 to 20 days.
Final conversion to calcitriol takes place in the kidney proximal tubules, and to lesser extent in the placenta, macrophages, lymphatic system cells and concerns the position 1α. The activity of 1α-hydroxylase $25(OH)D_3$ in kidneys is regulated by hormonal and metabolic pathways. The increased activity of this enzyme cause: parathormone, prolactin, growth hormone, sex hormones, insulin, PGE_2 prostaglandin.
Increased activity of this enzyme was also reported in children who are deficient in vitamin D_3, calcium and phosphates in the diet. Decreased activity of 1α-hydroxylase cause: cortisone, thyroxine, metabolic acidosis, ethanol and increased concentration of calcium and phosphates in blood. The alternative metabolite of calcidiol is 24,25-dihydroxycholecalciferol [$24,25(OH)D_3$] formed in kidneys with sufficient concentration of calcium and active metabolites of vitamin D_3. It is characterized by the minor metabolic activity. $1,25(OH)_2D_3$ is a regulator of its own biotransformation; it induces 24-hydroxylase, and inhibits 1α-hydroxylase. During the metabolism of vitamin D_3 1,24,25-trihydroxycholecalciferol and 25,26-dihydroxycholecalciferol may be formed.
Part of hydroxyl metabolites (about 25% of dose) are bounded to glucuronic or sulphuric acid and then excreted with bile.

Elimination
Vitamin D_3 and its active metabolites are bounded to glucuronic acid, glycine and taurine in the liver, then excreted with bile. Only small amounts are excreted with urine. Small amount of vitamin D_3 is excreted to human milk.

5.3 Preclinical safety data

Scientific literature data indicate that the limitation in the use of cholecalciferol results mainly from the teratogenic properties of the active substance observed at doses 2500 IU/kg and higher. Safety of use is a result of the amount of single and daily dose and duration of exposure, as well as thorough assessment of state of vitamin and mineral homeostasis and the degree of coverage of the demand for this vitamin in diet.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline (type 102)
Calcium hydrogen phosphate dihydrate
Pregelatinized starch, maize
Crospovidone (type A)
Sucrose
Magnesium stearate
Sodium ascorbate
Medium chain triglycerides of saturated fatty acids
Silica, colloidal anhydrous
all-*rac*-*α*-Tocopherol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

12 months

6.4 Special precautions for storage

Store below 30ºC.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters placed into a cardboard box.

Pack sizes: 60 or 90 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIOFARM Sp. z o.o.
13, Wałbrzyska str.
60-198 Poznań – Poland

8. MARKETING AUTHORISATION NUMBER(s)

Vigalex Max, 1000 micrograms (4000 IU) - MA No.:

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT