

## Vitamin D Substances

Vitamina D.

The term vitamin D is used for a range of closely related sterol compounds including alfalcidol, calcifediol, calcitriol, colecalciferol, dihydrotachysterol, and ergocalciferol. Newer vitamin D analogues include doxercalciferol, falecalcitriol, maxacalcitol, and paricalcitol.

### Alfalcidol (BAN, rINN)

Alfalcidolum; Alfalcidol; Alfalcidolis; Alfakalsidol; Alfakalsidoli; EB-644;  $1\alpha$ -Hydroxycholecalciferol;  $1\alpha$ -Hydroxyvitamin D<sub>3</sub>;  $1\alpha$ -OH-D<sub>3</sub>; (5Z,7E)-9,10-Secosterolesta-5,7,10(19)-triene- $1\alpha$ ,3 $\beta$ -diol.

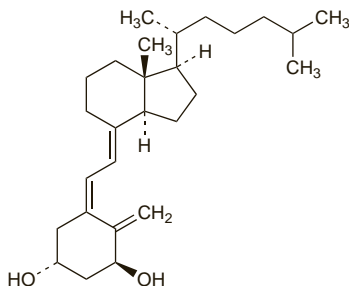
Альфакальцидол

$C_{27}H_{44}O_2 = 400.6$ .

CAS — 41294-56-8.

ATC — A11CC03.

ATC Vet — QA11CC03.



**Pharmacopoeias.** In *Chin.* and *Eur.* (see p.vii).

**Ph. Eur. 6.2** (Alfalcidol). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Reversible isomerisation to pre-alfalcidol takes place in solution, depending on temperature and time. Activity is due to both compounds. Store at 2° to 8° under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

### Calcifediol (BAN, USAN, rINN)

Calcidiol; Calcifédiol; Calcifediolum; Calcifediolum Monohydratum; 25-Hydroxycholecalciferol; 25-Hydroxyvitamin D<sub>3</sub>; Kalcifediol; Calcifedioli monohydrát; Kalcifediolis; Kalcifedioli; Kalsifedioli; 25-(OH)D<sub>3</sub>; U-32070E; (5Z,7E)-9,10-Secosterolesta-5,7,10(19)-triene-3 $\beta$ ,25-diol monohydrate.

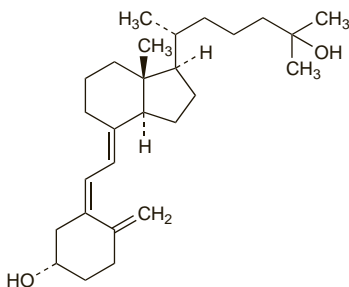
Кальцифедиол

$C_{27}H_{44}O_2 \cdot H_2O = 418.7$ .

CAS — 19356-17-3 (anhydrous calcifediol); 63283-36-3 (calcifediol monohydrate).

ATC — A11CC06.

ATC Vet — QA11CC06.



**Pharmacopoeias.** In *Eur.* (see p.vii) and *US*.

**Ph. Eur. 6.2** (Calcifediol). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Reversible isomerisation to pre-calcifediol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store at 2° to 8° under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

**USP 31** (Calcifediol). Store in airtight containers. Protect from light.

### Calcitriol (BAN, USAN, rINN)

Calcitriolum; 1,25-Dihydroxycholecalciferol;  $1\alpha,25$ -Dihydroxycholecalciferol;  $1\alpha,25$ -Dihydroxyvitamin D<sub>3</sub>; Kalcitriol; Kalcitriolis; Kalsitriol; Kalsitrioli;  $1\alpha,25$ (OH)<sub>2</sub>D<sub>3</sub>; Ro-21-5535; (5Z,7E)-9,10-Secosterolesta-5,7,10(19)-triene- $1\alpha$ ,3 $\beta$ ,25-triol.

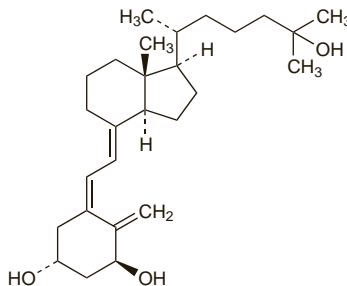
Кальцитриол

$C_{27}H_{44}O_3 = 416.6$ .

CAS — 32222-06-3 (anhydrous); 77326-95-5 (monohydrate).

ATC — A11CC04; D05AX03.

ATC Vet — QA11CC04; QD05AX03.



**Pharmacopoeias.** In *Eur.* (see p.vii) and *US*.

**Ph. Eur. 6.2** (Calcitriol). White or almost white crystals. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. It is sensitive to air, heat, and light. A reversible isomerisation to pre-calcitriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store at 2° to 8° under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

**USP 31** (Calcitriol). It may be anhydrous or contain one molecule of hydration. White or almost white crystals. Practically insoluble in water; freely soluble in alcohol; soluble in ether and in fatty oils. Store in airtight containers. Protect from light.

### Colecalciferol (BAN, rINN)

Activated 7-Dehydrocholesterol; Colecalciferol; Cholecalciferol; Cholecalciferolum; Cholecalciferol; Cholecalciferolis; Cholecalciferol; Colecalciferoli; Colecalciferolum; Kolecalciferol; Kolecalciferoli; Vitamin D<sub>3</sub>; (5Z,7E)-9,10-Secosterolesta-5,7,10(19)-triene-3 $\beta$ -ol.

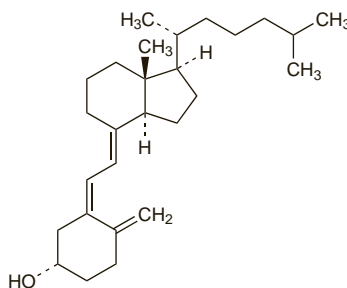
Колекальциферол

$C_{27}H_{44}O = 384.6$ .

CAS — 67-97-0.

ATC — A11CC05.

ATC Vet — QA11CC05.



**Description.** Colecalciferol is the naturally occurring form of vitamin D. It is produced from 7-dehydrocholesterol, a sterol present in mammalian skin, by ultraviolet irradiation.

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.*, *US*, and *Viet*.

*Eur.* also includes monographs for concentrates in an oily form, a powder form, and a water-dispersible form. *US* also includes a solution.

**Ph. Eur. 6.2** (Cholecalciferol; Colecalciferol BP 2008). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in trimethylpentane and in fatty oils. Solutions in solvents without an antioxidant are unstable and should be used immediately. A reversible isomerisation to pre-colecalciferol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store under nitrogen in airtight containers at a temperature of 2° to 8°. The contents of an opened container should be used immediately. Protect from light.

The BP 2008 directs that when calciferol or vitamin D is prescribed or demanded, Colecalciferol or Ergocalciferol shall be

dispensed or supplied.

**Ph. Eur. 6.2** (Cholecalciferol Concentrate (Oily Form); Cholecalciferolum Densatum Oleosum; Colecalciferol Concentrate (Oily Form) BP 2008). A solution of colecalciferol in a suitable vegetable oil. It contains not less than 500 000 units/g. It may contain suitable stabilisers such as antioxidants. A clear, yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; miscible with solvents of fats. Partial solidification may occur, depending on the temperature. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of nitrogen.

**Ph. Eur. 6.2** (Cholecalciferol Concentrate (Powder Form); Cholecalciferoli Pulvis; Colecalciferol Concentrate (Powder Form) BP 2008). It is obtained by dispersing an oily solution of colecalciferol in an appropriate matrix which is usually based on a combination of gelatin and carbohydrates of suitable quality. It contains not less than 100 000 units/g. It may contain suitable stabilisers such as antioxidants. White or yellowish-white, small particles. Depending on their formulation, it may be practically insoluble in water or may swell or form a dispersion. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of nitrogen.

**Ph. Eur. 6.2** (Cholecalciferol Concentrate (Water-dispersible Form); Cholecalciferolum in Aqua Dispersibile; Colecalciferol Concentrate (Water-dispersible Form) BP 2008). A solution of colecalciferol in a suitable vegetable oil to which suitable stabilisers have been added. It contains not less than 100 000 units/g. It may contain suitable stabilisers such as antioxidants. A slightly yellowish liquid of variable opalescence and viscosity. Highly concentrated solutions may become cloudy at low temperatures or form a gel at room temperature. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of inert gas.

**USP 31** (Cholecalciferol). White, odourless crystals. Insoluble in water; soluble in alcohol, in chloroform, and in fatty oils. M.p. about 85°. It is affected by air and light. Store under nitrogen in hermetically sealed containers at a temperature of 8° to 15°. Protect from light.

**USP 31** (Cholecalciferol Solution). A solution of colecalciferol in an edible vegetable oil, in polysorbate 80, or in propylene glycol. Store in airtight containers. Protect from light.

### Dihydrotachysterol (BAN, rINN)

Dichysterol; Dihidrotakisterol; Dihidrotakisterol; Dihydrotachysterol; Dihydrotachysterolum; Dihidrotakisterol; Dihydrotakysterol; Dihydrotakysteroli. (5E,7E,22E)-10 $\alpha$ -9,10-Secosterolesta-5,7,22-trien-3 $\beta$ -ol.

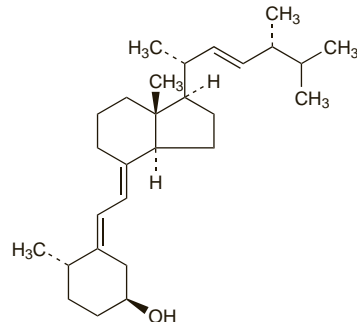
Дигидротакистерол

$C_{28}H_{46}O = 398.7$ .

CAS — 67-96-9.

ATC — A11CC02.

ATC Vet — QA11CC02.



**Pharmacopoeias.** In *Eur.* (see p.vii) and *US*.

**Ph. Eur. 6.2** (Dihydrotachysterol). Colourless crystals, or a white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in *n*-hexane. Store under an inert gas in airtight containers at 2° to 8°.

**USP 31** (Dihydrotachysterol). Colourless or white, odourless crystals, or white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform and in ether; sparingly soluble in vegetable oils. Store in hermetic glass containers from which the air has been displaced by an inert gas. Protect from light.

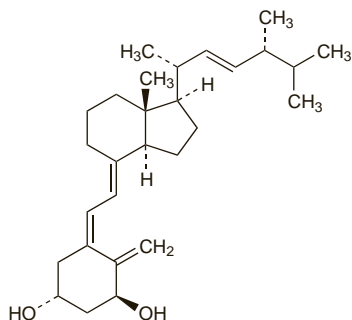
**Doxercalciferol** (USAN, rINN)

Doxercalciferol; Doxercalciferolum; 1 $\alpha$ -Hydroxyergocalciferol; 1 $\alpha$ -Hydroxyvitamin D<sub>2</sub>; 1 $\alpha$ -OH-D<sub>2</sub>; (5Z,7E,22E)-9,10-Secoergosta-5,7,10(19),22-tetraene-1 $\alpha$ ,3 $\beta$ -diol.

Доксэргальциферол

C<sub>28</sub>H<sub>44</sub>O<sub>2</sub> = 412.6.

CAS — 54573-75-0.

**Ergocalciferol** (BAN, rINN)

Calciferol; Ergocalciferol; Ergocalciferolum; Ergocalciferol; Ergocalciferolis; Ergokalsiferol; Ergokalsiferoli; Irradiated Ergosterol; Viosterol; Vitamin D<sub>2</sub>; (5Z,7E,22E)-9,10-Secoergosta-5,7,10(19),22-tetraen-3 $\beta$ -ol.

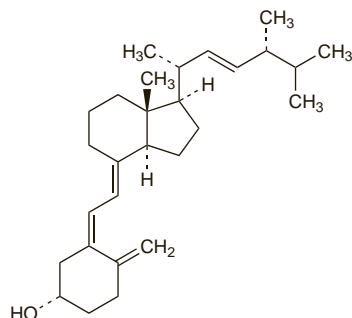
Эргокальциферол

C<sub>28</sub>H<sub>44</sub>O = 396.6.

CAS — 50-14-6.

ATC — A11CC01.

ATC Vet — QA11CC01.



**Description.** Ergocalciferol is an antirachitic substance obtained from ergosterol, a sterol present in fungi and yeasts, by ultraviolet irradiation.

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.*, *US*, and *Viet.*

**Ph. Eur. 6.2** (Ergocalciferol). White or almost white, crystals or white or slightly yellowish crystalline powder. It is sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Solutions in volatile solvents are unstable and should be used immediately. A reversible isomerisation to pre-ergocalciferol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store under nitrogen in airtight containers at a temperature of 2° to 8°. The contents of an opened container should be used immediately. Protect from light.

The BP 2008 directs that when calciferol or vitamin D is prescribed or demanded, Ergocalciferol or Colecalciferol shall be dispensed or supplied.

**USP 31** (Ergocalciferol). White, odourless crystals. It is affected by air and light. Insoluble in water; soluble in alcohol, in chloroform, in ether, and in fatty oils. Store in hermetically sealed containers under nitrogen at a temperature of 8° to 15°. Protect from light.

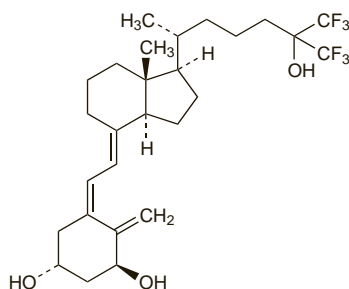
**Falecalcitriol** (rINN)

Falécaltitriol; Falecalcitriolum; Flocaltitriol; Hexafluorocaltitriol; Ro-23-4194; ST-630. (+)-(5Z,7E)-26,26,26,27,27-Hexafluoro-9,10-secocholesta-5,7,10(19)-triene-1 $\alpha$ ,3 $\beta$ ,25-triol.

Фалекальцитриол

C<sub>27</sub>H<sub>38</sub>F<sub>6</sub>O<sub>3</sub> = 524.6.

CAS — 83805-11-2.

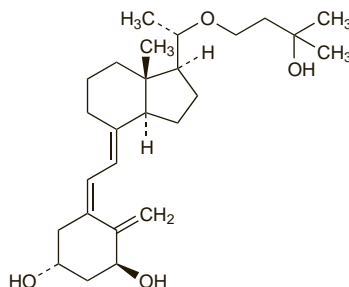
**Maxacalcitol** (USAN, rINN)

1 $\alpha$ ,25-Dihydroxy-22-oxavitamin D<sub>3</sub>; Maxacalcitolum; OCT; 22-Oxacalcitriol; Sch-209579. (+)-(5Z,7E,20S)-20-(3-Hydroxy-3-methylbutoxy)-9,10-secopregna-5,7,10(19)-triene-1 $\alpha$ ,3 $\beta$ -diol.

Максакальцитол

C<sub>26</sub>H<sub>42</sub>O<sub>4</sub> = 418.6.

CAS — 103909-75-7.

**Paricalcitol** (USAN, rINN)

ABT-358; Compound 49510; Paralcin; Paricalcitolum. (7E,22E)-19-Nor-9,10-secoergosta-5,7,22-triene-1 $\alpha$ ,3 $\beta$ ,25-triol.

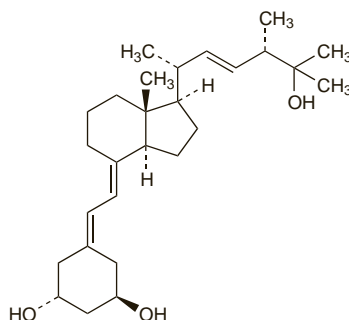
Парикальцитол

C<sub>27</sub>H<sub>44</sub>O<sub>3</sub> = 416.6.

CAS — 131918-61-1.

ATC — A11CC07.

ATC Vet — QA11CC07.



**Pharmacopoeias.** In *US*.

**USP 31** (Paricalcitol). A white to almost white powder. Insoluble in water; soluble in alcohol. Store under argon in airtight containers at a temperature of -25° to -10°.

**Units**

The Second International Standard Preparation (1949) of vitamin D consisted of bottles containing about 6 g of a solution of colecalciferol in vegetable oil (1000 units/g). This standard has now been discontinued.

**NOTE.** Pharmacopoeias consider that one unit of vitamin D is contained in 25 nanograms of colecalciferol or ergocalciferol (i.e. 1 mg of colecalciferol or ergocalciferol is equivalent to 40 000 units of vitamin D as determined by bioassay in *rats*), but see below.

**Equivalence.** It has been proposed that units of vitamin D be defined in moles or molecules rather than weight terms; in which case, 1 unit of colecalciferol and ergocalciferol would be equivalent to 25 nanograms and 25.78 nanograms, respectively. This inequivalence in units might confound optimal vitamin D dosing

recommendations.<sup>1</sup> For the view that colecalciferol is more potent than ergocalciferol, and should be preferred for vitamin D supplementation, see Administration, below.

1. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D<sub>2</sub>) as a vitamin supplement. *Am J Clin Nutr* 2006; **84**: 694-7.

**Adverse Effects and Treatment**

Excessive intake of vitamin D leads to the development of hyperphosphataemia or hypercalcaemia. Associated effects of hypercalcaemia include hypercalcaemia, ectopic calcification, and renal and cardiovascular damage (for a discussion of vitamin-D mediated hypercalcaemia and its treatment, see p.1668). Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence, and vertigo. Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin should be withdrawn if toxicity occurs. It has been stated that vitamin D dietary supplementation may be detrimental in persons already receiving an adequate intake through diet and exposure to sunlight, since the difference between therapeutic and toxic concentrations is relatively small.

The most potent forms of vitamin D, such as alfalcidol and calcitriol, might reasonably be expected to pose a greater risk of toxicity; however, their effects are reversed rapidly on withdrawal.

Hypersensitivity reactions have occurred. Skin irritation or contact dermatitis has been reported with topical preparations.

**Hypercalcaemia.** Vitamin D is the most likely of all vitamins to cause overt toxicity. Doses of 60 000 units daily can cause hypercalcaemia (p.1668), with muscle weakness, apathy, headache, anorexia, nausea and vomiting, bone pain, ectopic calcification, proteinuria, hypertension, and cardiac arrhythmias. Chronic hypercalcaemia can lead to generalised vascular calcification, nephrocalcinosis, and rapid deterioration of renal function.<sup>1,2</sup> A number of reports of accidental overdosage, leading to hypercalcaemia or nephrocalcinosis, occurred in the UK after introduction of a concentrated alfalcidol oral solution that was 10 times stronger than the former presentation.<sup>3</sup>

Hypercalcaemia has been reported in a patient after brief industrial exposure to colecalciferol.<sup>4</sup>

A study in children treated for renal osteodystrophy has provided some evidence that hypercalcaemia may occur more frequently with calcitriol than with ergocalciferol.<sup>5</sup> Another such study has suggested that vitamin D has nephrotoxic properties independent of the degree of induced hypercalcaemia, and that the decline in renal function may be more marked with calcitriol.<sup>6</sup>

Topical calcitriol may affect calcium homeostasis, and hypercalcaemia has been reported in some studies.<sup>7</sup> For reference to the effect of other vitamin D analogues used in psoriasis on calcium homeostasis, see p.1591.

1. Anonymous. Toxic effects of vitamin overdosage. *Med Lett Drugs Ther* 1984; **26**: 73-4.

2. Chiricone D, *et al.* Unusual cases of chronic intoxication by vitamin D. *J Nephrol* 2003; **16**: 917-21.

3. Committee on Safety of Medicines/Medicines Control Agency. Accidental overdose with alfalcidol (One-Alpha drops). *Current Problems* 2001; **27**: 3. Also available at: [http://www.mhra.gov.uk/home/idcplg?ldcService=GET\\_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased](http://www.mhra.gov.uk/home/idcplg?ldcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased) (accessed 09/01/06)

4. Jibani M, Hodges NH. Prolonged hypercalcaemia after industrial exposure to vitamin D. *BMJ* 1985; **290**: 748-9.

5. Hodson EM, *et al.* Treatment of childhood renal osteodystrophy with calcitriol or ergocalciferol. *Clin Nephrol* 1985; **24**: 192-200.

6. Chan JCM, *et al.* A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. *J Pediatr* 1994; **124**: 520-8.

7. Bourke JF, *et al.* Vitamin D analogues in psoriasis: effects on systemic calcium homeostasis. *Br J Dermatol* 1996; **135**: 347-54.

**Precautions**

Vitamin D should not be given to patients with hypercalcaemia. It should be used with caution in infants, who may have increased sensitivity to its effects, and patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcaemia occurred. Plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification.

It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially