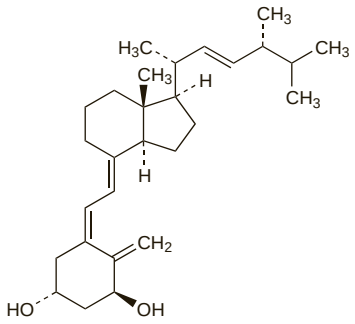
Doxercalciferol *(USAN, rINN)*

Doxercalciférol; Doxercalciferolum; 1α-Hydroxyergocalciferol; 1α-Hydroxyvitamin D_2; 1α-OH-D_2. (5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraene-1α,3β-diol.

Доксэркальциферол

$C_{28}H_{44}O_2$ = 412.6.

CAS — 54573-75-0.



Ergocalciferol *(BAN, rINN)*

Calciferol; Ergocalciférol; Ergocalciferolum; Ergokalciferol; Ergokalciferolis; Ergokalsiferol; Ergokalsiferoli; Irradiated Ergosterol; Viosterol; Vitamin D_2. (5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraen-3β-ol.

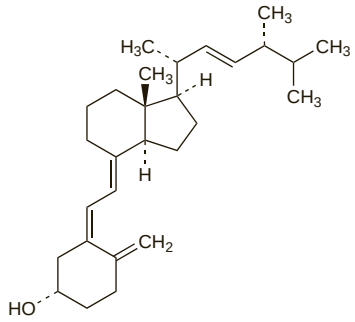
Эргокальциферол

$C_{28}H_{44}O$ = 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.

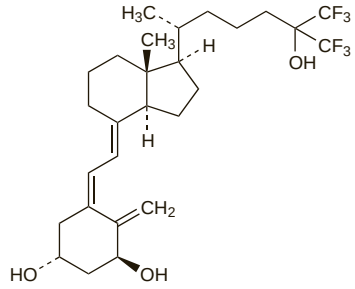
Falecalcitriol *(rINN)*

Falécalcitriol; Falecalcitriolum; Flocalcitriol; Hexafluorocalcitriol; Ro-23-4194; ST-630. (+)-(5*Z*,7*E*)-26,26,26,27,27,27-Hexafluoro-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol.

Фалекальцитриол

$C_{27}H_{38}F_6O_3$ = 524.6.

CAS — 83805-11-2.



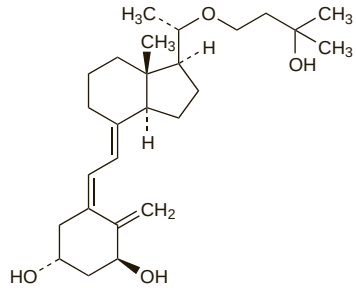
Maxacalcitol *(USAN, rINN)*

1α,25-Dihydroxy-22-oxavitamin D_3; Maxacalcitolum; OCT; 22-Oxacalcitriol; Sch-209579. (+)-(5*Z*,7*E*,20*S*)-20-(3-Hydroxy-3-methylbutoxy)-9,10-secopregna-5,7,10(19)-triene-1α,3β-diol.

Максакальцитол

$C_{26}H_{42}O_4$ = 418.6.

CAS — 103909-75-7.



Paricalcitol *(USAN, rINN)*

ABT-358; Compound 49510; Paracalcin; Paricalcitolum. (7*E*,-22*E*)-19-Nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol.

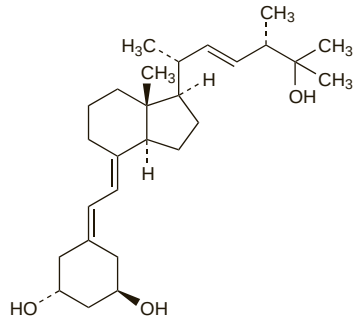
Парикальцитол

$C_{27}H_{44}O_3$ = 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.[1] 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) 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 hypercalciuria, 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 alfacalcidol 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.[1,2] A number of reports of accidental overdosage, leading to hypercalcaemia or nephrocalcinosis, occurred in the UK after introduction of a concentrated alfacalcidol oral solution that was 10 times stronger than the former presentation.[3]

Hypercalcaemia has been reported in a patient after brief industrial exposure to colecalciferol.[4]

A study in children treated for renal osteodystrophy has provided some evidence that hypercalcaemia may occur more frequently with calcitriol than with ergocalciferol.[5] 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.[6]

Topical calcitriol may affect calcium homoeostasis, and hypercalcaemia has been reported in some studies.[7] For reference to the effect of other vitamin D analogues used in psoriasis on calcium homoeostasis, 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 alfacalcidol (One-Alpha drops). *Current Problems* 2001; **27:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=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

initially or if symptoms suggest toxicity (see above). Similar monitoring is recommended in infants if they are breast fed by mothers receiving pharmacological doses of vitamin D (see below).

Breast feeding. Vitamin D is distributed into breast milk,[1] and its concentration appears to correlate with the amount of vitamin D in the serum of exclusively breast-fed infants.[2] The American Academy of Pediatrics considers the use of vitamin D to be usually compatible with breast feeding,[3] although they and others[4] recommend that the infant be closely monitored for hypercalcaemia or clinical manifestations of vitamin D toxicity if the mother is taking pharmacological doses of vitamin D.

1. Rothberg AD, *et al.* Maternal-infant vitamin D relationships during breast-feeding. *J Pediatr* 1982; **101:** 500–503.
2. Cancela L, *et al.* Relationship between the vitamin D content of maternal milk and the vitamin D status of nursing women and breast-fed infants. *J Endocrinol* 1986; **110:** 43–50.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)
4. Greer FR, *et al.* High concentrations of vitamin D in human milk associated with pharmacologic doses of vitamin D . *J Pediatr* 1984; **105:** 61–4.

Pregnancy. Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy. Indeed, one report noted increased requirements for vitamin D preparations during pregnancy for the treatment of hypoparathyroidism;[1] the dose needed tended to increase during the second half of pregnancy. In one woman in whom the dose of calcitriol remained raised after delivery (in an attempt to allow for the calcium loss involved in breast feeding) hypercalcaemia developed; this did not occur in 2 women who did not breast feed and in whom the dose of the vitamin D preparations was reduced soon after delivery.[1] For discussions regarding vitamin D requirements during pregnancy, see UK and US recommended dietary intake, p.1988, and Pregnancy and the Neonate, p.1991, below.

1. Caplan RH, Beguin EA. Hypercalcemia in a calcitriol-treated hypoparathyroid woman during lactation. *Obstet Gynecol* 1990; **76:** 485–9.

Interactions

There is an increased risk of hypercalcaemia if vitamin D is given with thiazide diuretics, calcium, or phosphate. Plasma-calcium concentrations should be monitored in such situations. Some antiepileptics may increase vitamin D requirements (e.g. carbamazepine, phenobarbital, phenytoin, and primidone). Rifampicin and isoniazid may reduce the effectiveness of vitamin D. Corticosteroids may counteract the effect of vitamin D. Ketoconazole may inhibit the metabolism of paricalcitol and these drugs should be used with caution together; care should be taken when using paricalcitol with other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4.

Danazol. A report of hypercalcaemia associated with danazol in a patient maintained on alfacalcidol therapy for hypoparathyroidism.[1] Introduction of danazol appeared to reduce the maintenance requirement for alfacalcidol.

1. Hepburn NC, *et al.* Danazol-induced hypercalcaemia in alphacalcidol-treated hypoparathyroidism. *Postgrad Med J* 1989; **65:** 849–50.

Levothyroxine. Three patients taking dihydrotachysterol and calcium, for postoperative hypoparathyroidism after thyroidectomy, as well as levothyroxine, developed hypercalcaemia when the latter was stopped before a radio-iodine scan.[1] The dose of dihydrotachysterol should be reduced and serum-calcium concentrations should be monitored when thyroid treatment is interrupted, since elimination of dihydrotachysterol may be delayed in hypothyroidism.

1. Lamberg B-A, Tikkanen MJ. Hypercalcaemia due to dihydrotachysterol treatment in patients with hypothyroidism after thyroidectomy. *BMJ* 1981; **283:** 461–2.

Pharmacokinetics

Vitamin D substances are well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption; absorption may be decreased in patients with decreased fat absorption.

Vitamin D and its metabolites circulate in the blood bound to a specific α-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Ergocalciferol and colecalciferol have a slow onset and a long duration of action; calcitriol and its analogue alfacalcidol, however, have a more rapid action and shorter half-lives.

Colecalciferol and ergocalciferol are hydroxylated in the liver by the enzyme vitamin D 25-hydroxylase to form 25-hydroxycholecalciferol (calcifediol) and 25-hydroxyergocalciferol respectively. These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D 1-hydroxylase to form the active metabolites 1,25-dihydroxycholecalciferol (calcitriol) and 1,25-dihydroxyergocalciferol respectively. Further metabolism also occurs in the kidneys, including the formation of the 1,24,25-trihydroxy derivatives. Of the synthetic analogues, alfacalcidol, dihydrotachysterol, and doxercalciferol are converted directly in the liver to their active metabolites (calcitriol, 25-hydroxydihydrotachysterol, and 1,25-dihydroxyergocalciferol respectively).

Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

Human Requirements

The daily requirements of vitamin D in adults are small and may be met mainly by exposure to sunlight and/or obtained from the diet. A daily dietary intake of about 200 to 400 units (5 to 10 micrograms of colecalciferol or ergocalciferol) of vitamin D is generally considered adequate for healthy adults. In comparison with older adults (in the age range of 25 years upwards) the requirements per kg body-weight are greater in infants, children, and young adults and during pregnancy and lactation. Requirements may also be higher in people who are not exposed to adequate sunlight such as the elderly or housebound.

Vitamin D is present in few foods. Fish-liver oils, especially cod-liver oil, are good sources of vitamin D. Other sources, which contain much smaller amounts, include butter, eggs, and liver. Some foods are fortified with vitamin D, and milk and margarine may therefore also supply the vitamin. Cooking processes do not appear to affect the activity of vitamin D.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) for vitamin D have only been published for selected groups of the population.[1] In the USA recommended dietary allowances had been set, and were subsequently replaced by dietary reference intakes[2] (see p.1925). Differing amounts are recommended for infants and children of varying ages, for adults, and for pregnant and lactating women. In the UK a dietary intake was considered unnecessary for adults living a normal lifestyle who were being exposed to solar radiation; for those confined indoors a reference nutrient intake (RNI) of 10 micrograms (400 units) [as colecalciferol or ergocalciferol] daily was set. This RNI of 10 micrograms daily was also considered to be applicable to all persons aged 65 years or more and to pregnant and lactating women. RNIs were set for children up to the age of 3 years; dietary intake was considered unnecessary for older children. Mention was made that in order to achieve the above reference nutrient intakes, supplementation of the diet may actually be required and supplementation was also recommended for Asian [i.e. from the Indian subcontinent] women and children in the UK (see also Pregnancy and the Neonate, below). In the USA,[2] adequate intakes for vitamin D are: 5 micrograms (200 units) daily (as colecalciferol) for all persons from birth through to age 50 years, including pregnant or lactating women; 10 micrograms daily for adults aged 51 to 70 years; and 15 micrograms daily for those aged greater than 70 years. The tolerable upper intake level is 50 micrograms (2000 units) daily. The 2005 Dietary Guidelines for Americans (published jointly by the US Department of Health and Human Services, and the US Department of Agriculture) recommend that high-risk groups including the elderly, those with dark skin, and those exposed to insufficient UV radiation, consume daily intakes of 25 micrograms (1000 units) daily.[3] The definition of vitamin D deficiency and vitamin D insufficiency remains controversial in terms of serum vitamin D concentrations.[4,5] Because vitamin D insufficiency is considered to be common in northern latitudes,[5] and deficiency is increasing worldwide,[4] higher intakes than those mentioned above have been recommended. Some have called for the establishment of an estimated average requirement (EAR) in North America,[4] and estimate a recommended dietary allowance (RDA) of greater than 12.5 micrograms (500 units). Others[5] suggest that the adequate intake be increased to at least 20 to 25 micrograms (800 to 1000 units) daily. A risk assessment analysis concluded that the tolerable upper intake level of vitamin D could be increased to 250 micrograms (10 000 units) daily for the general healthy population.[6]

The consensus of over 300 scientists from 23 countries at a vitamin D workshop was that governmental guidelines, in all countries, with respect to daily vitamin D requirements (to maintain bone health and health in general) were too low and did not reflect advances in vitamin D research over the preceding decade. Eating vitamin D-rich foods does not solve vitamin D deficiency for most adults; fortification of food should be significantly improved and implemented. Recommendations were made that blood concentrations of vitamin D should be at least 20 nanograms/mL, and that the tolerable upper intake level of 50 micrograms (2000 units) be re-evaluated in light of new data.[7]

For the view that colecalciferol is more potent than ergocalciferol, and should be the preferred form of vitamin D supplementation, see Administration, below.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)
3. US Department of Health and Human Services/US Department of Agriculture. Dietary Guidelines for Americans 2005. Available at: http://www.health.gov/DIETARYGUIDELINES/dga2005/document/pdf/DGA2005.pdf (accessed 10/09/07)
4. Whiting SJ, Calvo MS. Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement. *J Nutr* 2005; **135:** 304–9.
5. Hanley DA, Davison KS. Vitamin D insufficiency in North America. *J Nutr* 2005; **135:** 332–7.
6. Hathcock JN, *et al.* Risk assessment for vitamin D. *Am J Clin Nutr* 2007; **85:** 6–18.
7. Norman AW, *et al.* 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol* 2007; **103:** 204–5.

Uses and Administration

Vitamin D compounds are fat-soluble sterols, sometimes considered to be hormones or hormone precursors, which are essential for the proper regulation of calcium and phosphate homoeostasis and bone mineralisation.

Vitamin D deficiency develops when there is inadequate exposure to sunlight or a lack of the vitamin in the diet. Deficiency generally takes a long time to develop because of slow release of the vitamin from body stores. It may occur in some infants who are breast fed without supplemental vitamin D or exposure to sunlight, in the elderly whose mobility and thus exposure to light may be impaired, and in persons with fat malabsorption syndromes; certain disease states such as renal failure may also affect the metabolism of vitamin D substances to metabolically active forms and thus result in deficiency.

Deficiency leads to the development of a syndrome characterised by hypocalcaemia, hypophosphataemia, undermineralisation or demineralisation of bone, bone pain, bone fractures, and muscle weakness, known in adults as osteomalacia (see below). In children, in whom there may be growth retardation and skeletal deformity, especially of the long bones, it is known as rickets.

Vitamin D compounds are used in the treatment and prevention of vitamin D deficiency states and hypocalcaemia in disorders such as hypoparathyroidism and secondary hyperparathyroidism, as indicated by the cross-references given below.

Many forms and analogues of vitamin D are available, and the choice of agent depends on the cause of the condition to be treated and the relative properties of the available agents. Colecalciferol and ergocalciferol are traditionally considered equal in potency (but see Administration, below), and have a slow onset and relatively prolonged duration of action. Dihydrotachysterol has relatively weak antirachitic activity, but its actions are faster in onset and less persistent than those of the calciferols and it does not require renal hydroxylation. Calcifediol, an intermediate metabolite, has some action of its own but is also converted to the more potent 1,25-dihydroxycholecalciferol (calcitriol); cal-

citriol and its analogue alfacalcidol are the most potent and rapidly acting of the vitamin D substances.

- For the treatment of simple nutritional deficiencies **colecalciferol** or **ergocalciferol** are generally preferred. They are usually given orally, but may also be given by intramuscular injection. A dose of 10 micrograms (400 units) daily is generally sufficient in adults for the prevention of simple deficiency states; in the UK, 20 micrograms (800 units) daily is recommended in those whose exposure to sunlight is limited, in those whose diet is deficient in vitamin D, and in housebound or institutionalised elderly people. Deficiency due to malabsorption states or liver disease often requires higher doses for treatment, of up to 1 mg (40 000 units) daily. Doses of up to 5 mg (200 000 units) daily may be used in the treatment of hypocalcaemia due to hypoparathyroidism.
- Where large doses are required it may be preferable to use one of the more potent derivatives. In particular, when renal function is impaired as in secondary hyperparathyroidism associated with chronic renal failure, with consequent reduction in the conversion of calciferols to their active metabolites, then a drug such as alfacalcidol, calcitriol, doxercalciferol, maxacalcitol, or paricalcitol, which does not require renal hydroxylation, should be given.

Calcitriol is given orally or by intravenous injection. Usual initial adult oral doses of 250 nanograms daily or on alternate days are given, increased if necessary, in steps of 250 nanograms at intervals of 2 to 4 weeks, to a usual dose of 0.5 to 1 microgram daily. Initial doses intravenously are usually 500 nanograms three times a week increased if necessary in steps of 250 to 500 nanograms at intervals of 2 to 4 weeks, to a usual dose of 0.5 to 3 micrograms three times a week. For moderate to severe secondary hyperparathyroidism in dialysis patients initial doses of 0.5 to 4 micrograms have been given three times a week, increased if necessary in steps of 250 nanograms to 1 microgram at intervals of 2 to 4 weeks to a maximum of 8 micrograms given three times a week.

Alternatively, **alfacalcidol** is given in initial oral doses of 1 microgram daily, or 500 nanograms for elderly patients. Doses of 0.25 to 1 microgram daily may be given for maintenance. Suggested doses for children under 20 kg are 50 nanograms/kg daily and for premature infants and neonates a dose of 50 to 100 nanograms/kg daily. Doses of alfacalcidol may also be given by intravenous injection over 30 seconds.

Doxercalciferol is given orally or by intravenous injection. The initial oral dose is 10 micrograms three times weekly at dialysis, increased by increments of 2.5 micrograms after 8 weeks if necessary. The maximum recommended oral dose is 20 micrograms three times weekly. The initial intravenous dose is 4 micrograms given three times weekly at dialysis, and increased after 8 weeks in increments of 1 to 2 micrograms if required. Doses are titrated according to parathyroid hormone concentrations.

Maxacalcitol is given intravenously at a dose of 2.5 to 10 micrograms three times weekly; the dose may be gradually increased if necessary, to a maximum of 20 micrograms three times weekly.

Paricalcitol is given intravenously in the USA at a dose of 40 to 100 nanograms/kg on alternate days or less frequently; in the UK the initial dose (in micrograms) is calculated by dividing the baseline intact parathyroid hormone concentration (in picograms/mL) by 80. The dose may be increased or decreased if necessary by 2 to 4 micrograms at intervals of 2 to 4 weeks, based on parathyroid hormone concentrations. Paricalcitol is also given orally either as a daily dose or three times weekly (no more frequently than every other day). Again, the initial dose is based on baseline intact parathyroid hormone concentrations. If these are 500 picograms/mL or less, paricalcitol is given at a dose of 1 microgram daily, or 2 micrograms three times weekly; if they are above 500 picograms/mL, paricalcitol 2 micrograms daily, or 4 micrograms three times weekly is suggested. Doses are titrated according to parathyroid hormone concentrations.

- Of the other available forms, **calcifediol**, the 25-hydroxylated metabolite of colecalciferol, has been given in usual adult oral doses of 50 to 100 micrograms daily or 100 to 200 micrograms on alternate days. For hypocalcaemic tetany due to hypoparathyroidism, **dihydrotachysterol** is given in initial adult oral doses of 250 to 2400 micrograms daily, depending on severity, for about three days. Maintenance doses have ranged from 250 micrograms weekly to 1000 micrograms daily.

When vitamin D substances are given in pharmacological doses, dosage must be individualised for each patient, and should be based on regular monitoring of plasma-calcium concentrations (initially once or twice weekly), to optimise clinical response and avoid hypercalcaemia.

Vitamin D, usually in the form of calcitriol, may be used in the treatment of osteoporosis (see below). In established postmenopausal osteoporosis, calcitriol 0.25 micrograms twice daily is recommended. Vitamin D and calcium supplements are often given as adjuncts to other therapies in osteoporosis.

Calcitriol has been used in the management of psoriasis (see below).

Calciferol derivatives are used as rodenticides.

◊ General references.

1. Thomas MK, Demay MB. Vitamin D deficiency and disorders of vitamin D metabolism. *Endocrinol Metab Clin North Am* 2000; **29:** 611–27.
2. Fuller KE, Casparain JM. Vitamin D: balancing cutaneous and systemic considerations. *South Med J* 2001; **94:** 58–64.
3. Holick MF. Vitamin D: a millenium perspective. *J Cell Biochem* 2003; **88:** 296–307.
4. Holick MF. Vitamin D: importance in the prevention of cancers, type I diabetes, heart disease, and osteoporosis. *Am J Clin Nutr* 2004; **79:** 362–71.
5. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr* 2003; **89:** 552–72.
6. Heaney RP. Vitamin D, nutritional deficiency, and the medical paradigm. *J Clin Endocrinol Metab* 2003; **88:** 5107–8.
7. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* 2004; **80** (suppl): 1678S–1688S.
8. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004; **80** (suppl): 1689S–1696S.
9. Calvo MS, *et al.* Vitamin D intake: a global perspective of current status. *J Nutr* 2005; **135:** 310–16.
10. Bandeira F, *et al.* Vitamin D deficiency: a global perspective. *Arq Bras Endocrinol Metabol* 2006; **50:** 640–6.
11. Mason P. Vitamin D—function and uses. *Pharm J* 2006; **277:** 227–30.
12. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; **357:** 266–81.
13. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008; **87:** 1080S–1086S.

Administration. Minor differences in the chemistry of the side-chains of ergocalciferol and colecalciferol lead to the production of different metabolites (see Pharmacokinetics, above).[1] Colecalciferol has been reported to raise serum vitamin D concentrations more effectively than ergocalciferol,[2,3] perhaps because of higher affinities of colecalciferol and its metabolites for liver enzymes, plasma vitamin D binding protein, and vitamin D receptors.[1] It has been suggested that 50 000 units of ergocalciferol should be considered equivalent to no more than 15 000 units of colecalciferol, and perhaps closer to 5000 units; the tolerable upper intake level (see UK and US recommended dietary intake, p.1988) ought not to be applied to ergocalciferol.[3] These differences and the inequivalence in units (see Equivalence, under Units, above) may confound optimal vitamin D dosing recommendations.[1,3] The form of vitamin D used in studies should be specified.[2] While ergocalciferol is effective in treating vitamin D deficiency, the differences in potency have led some to suggest that colecalciferol be used as the preferred form of vitamin D.[1,3]

1. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D) as a vitamin supplement. *Am J Clin Nutr* 2006; **84:** 694–7.
2. Trang HM, *et al.* Evidence that vitamin D increases serum 25-hydroxyvitamin D more efficiently than does vitamin D . *Am J Clin Nutr* 1998; **68:** 854–8.
3. Armas LAG, *et al.* Vitamin D is much less effective than vitamin D in humans. *J Clin Endocrinol Metab* 2004; **89:** 5387–91.

Administration in the elderly. Vitamin D deficiency is common in the elderly,[1-3] especially in housebound patients, and during wintertime.[4] Deficiency is aggravated by a diet low in calcium,[1] lack of sunlight exposure, and decreasing ability of the skin to synthesise vitamin D with advancing age.[3,5] Elderly patients are therefore at risk of secondary hyperparathyroidism, bone loss and osteoporosis, and fractures.[1,6,7] Low serum vitamin D has been associated with increased fracture rates, and there is some evidence from *animal* studies that vitamin D may promote bone healing after fracture, increasing the mechanical strength of bone by promoting mineralisation.[7] Poor muscle strength and weakness may be associated with vitamin D deficiency, and may increase the risk of falling in the elderly.[2,8,9] A meta-analysis[10] of 5 studies found that vitamin D supplementation reduced the risk of falls in the elderly by 22% compared with calcium or placebo. Vitamin D deficiency in the elderly may be less prevalent in the USA, due to fortification of food.[1] Food fortification has therefore been recommended,[1] or supplementation with doses in the region of 10 to 20 micrograms (400 to 800 units) daily;[1,4] 20 micrograms (800 units) daily is considered necessary for reduction of falls and fractures in the elderly.[2,7,11] The 2005 Dietary Guidelines for Americans recommend that elderly people should consume 25 micrograms (1000 units) daily; the upper level of 50 micrograms (2000 units) should not be exceeded.[5] See also Osteomalacia, and Osteoporosis, below.

1. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2001; **22:** 477–501.
2. Venning G. Recent developments in vitamin D deficiency and muscle weakness among elderly people. *BMJ* 2005; **330:** 524–6.
3. Allain TJ, Dhesi J. Hypovitaminosis D in older adults. *Gerontology* 2003; **49:** 273–8.
4. Compston JE. Vitamin D deficiency: time for action. *BMJ* 1998; **317:** 1466–7.
5. Johnson MA, Kimlin MG. Vitamin D, aging, and the 2005 Dietary Guidelines for Americans. *Nutr Rev* 2006; **64:** 410–21.
6. Passeri G, *et al.* Low vitamin D status, high bone turnover, and bone fractures in centenarians. *J Endocrinol Metab* 2003; **88:** 5109–15.
7. Simon J, *et al.* Fractures in the elderly and vitamin D. *J Nutr Health Aging* 2002; **6:** 406–12.
8. Mosekilde L. Vitamin D and the elderly. *Clin Endocrinol (Oxf)* 2005; **62:** 265–81.
9. Janssen HCJP, *et al.* Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr* 2002; **75:** 611–15.
10. Bischoff-Ferrari HA, *et al.* Effect of vitamin D on falls: a meta-analysis. *JAMA* 2004; **291:** 1999–2006.
11. Bischoff-Ferrari HA, *et al.* Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 2005; **293:** 2257–64.

Cardiovascular disease. Myocardial tissue contains a vitamin D-dependent calcium-binding protein, indicating a role for vitamin D in the regulation of myocardial contractility.[1,2] Lack of vitamin D is considered to play a role in the aetiology and pathogenesis of cardiovascular disease such as congestive heart failure;[2] case reports have shown that vitamin D treatment reduced blood pressure and myocardial hypertrophy.[3] However, there is currently no rationale to prescribe specific vitamin D analogues for patients with congestive heart failure.[2]

1. Luong KVQ, Nguyen LTH. Vitamin D and cardiovascular disease. *Curr Med Chem* 2006; **13:** 2443–7.
2. Zittermann A, *et al.* Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev* 2006; **11:** 25–33.
3. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol* 2006; **92:** 39–48.

Diabetes mellitus. Vitamin D has a role in glucose homoeostasis and in the mechanism of insulin release.[1] Cohort studies[2,3] have suggested that supplementation with vitamin D may have a beneficial role in reducing the risk for developing both type 1 and type 2 diabetes mellitus. However, another study[4] found no significant differences in vitamin D status in Finnish or Karelian children, 2 neighbouring geographical areas with vastly differing incidences of type 1 diabetes.

1. Reis AF, *et al.* Vitamin D endocrine system and the genetic susceptibility to diabetes, obesity and vascular disease: a review of evidence. *Diabetes Metab* 2005; **31:** 318–25.
2. Hyppönen E, *et al.* Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001; **358:** 1500–1503.
3. Pittas AG, *et al.* Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006; **29:** 650–6.
4. Viskari H, *et al.* Circulating vitamin D concentrations in two neighboring populations with markedly different incidence of type 1 diabetes. *Diabetes Care* 2006; **29:** 1458–9.

Hyperparathyroidism. Vitamin D has been used for certain forms of hyperparathyroidism (p.1087). The **secondary hyperparathyroidism** of renal osteodystrophy (p.1086) may respond to treatment with calcitriol, or its analogue alfacalcidol,[1,2] which do not require renal hydroxylation for activation. Calcitriol has been used orally,[3] intravenously,[3,4] and intraperitoneally;[5] percutaneous injection directly into the parathyroid gland has also been reported to be safe and effective.[6-8] However, doses capable of suppressing parathyroid hormone secretion may lead to hypercalcaemia,[1-3,5,9,10] hyperphosphataemia,[1,2,5,9,10] and a decline in renal function;[11] the increase in calcium and phosphate may promote soft tissue and vascular calcification,[1,2] see Hypercalcaemia, under Adverse Effects, above.

Newer analogues for this indication include paricalcitol,[12-15] doxercalciferol,[16-18] falecalcitriol,[19] and maxacalcitol.[20-25] These are reported to have less effect on calcium and phosphate concentrations, while retaining the suppressive effect on parathyroid hormone;[1,5,9,10] however, some[2,18] consider clinically relevant benefit to be lacking. Paricalcitol was found to have a faster ef-

fect and cause less hypercalcaemia than calcitriol in patients on haemodialysis,[15] as well as offering a significant survival advantage over calcitriol.[13] A review considered paricalcitol to be as effective and as well tolerated as calcitriol.[14] Maxacalcitol and calcitriol were considered equally effective when given intravenously to haemodialysis patients,[25] while oral falecalcitriol was considered better than oral alfacalcidol at reducing parathyroid hormone concentrations.[19] Intravenous doxercalciferol appears to be safer than oral doxercalciferol;[1] comparative data are lacking.[2,18] A meta-analysis found that the use of vitamin D in chronic kidney disease did not consistently reduce parathyroid hormone concentrations.[26]

Some have cautioned against vitamin D supplementation in **primary hyperparathyroidism** because of concerns about exacerbation of hypercalcaemia and hypercalciuria. However, in a small study in patients with mild primary hyperparathyroidism, correction of vitamin D deficiency did not exacerbate hypercalcaemia, and decreased parathyroid hormone concentrations and bone turnover.[27]

1. Brown AJ, Coyne DW. Vitamin D analogs: new therapeutic agents for secondary hyperparathyroidism. *Treat Endocrinol* 2002; **1:** 313–27.
2. Cunningham J. New vitamin D analogues for osteodystrophy in chronic kidney disease. *Pediatr Nephrol* 2004; **19:** 705–8.
3. Quarles LD, *et al.* Prospective trial of pulse oral versus intravenous calcitriol treatment of hyperparathyroidism in ESRD. *Kidney Int* 1994; **45:** 1710–21.
4. Morosetti M, *et al.* High doses of intravenous calcitriol in the treatment of severe secondary hyperparathyroidism. *J Nephrol* 2004; **17:** 95–100.
5. Dusso AS, *et al.* Vitamin D receptor and analogs. *Semin Nephrol* 2004; **24:** 10–16.
6. Kitaoka M, *et al.* Percutaneous calcitriol injection therapy (PCIT) for secondary hyperparathyroidism: multicentre trial. *Nephrol Dial Transplant* 2003; **18** (suppl): iii38–iii41.
7. Shiizaki K, *et al.* Effect of percutaneous calcitriol injection therapy on secondary hyperparathyroidism in uraemic patients. *Nephrol Dial Transplant* 2003; **18** (suppl): iii42–iii46.
8. Nakanishi S, *et al.* Efficacy of direct injection of calcitriol into the parathyroid glands in uraemic patients with moderate to severe secondary hyperparathyroidism. *Nephrol Dial Transplant* 2003; **18** (suppl): iii47–iii49.
9. Martin KJ, González EA. Vitamin D analogs: actions and role in the treatment of secondary hyperparathyroidism. *Semin Nephrol* 2004; **24:** 456–9.
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11. 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.
12. Martin KJ, *et al.* Therapy of secondary hyperparathyroidism with 19-nor-1α,25-dihydroxyvitamin D . *Am J Kidney Dis* 1998; **32** (suppl 2): S61–6.
13. Teng M, *et al.* Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 2003; **349:** 446–56.
14. Robinson DM, Scott LJ. Paricalcitol: a review of its use in the management of secondary hyperparathyroidism. *Drugs* 2005; **65:** 559–76.
15. Sprague SM, *et al.* Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int* 2003; **63:** 1483–90.
16. Frazão JM, *et al.* Intermittent doxercalciferol (1α-hydroxyvitamin D) therapy for secondary hyperparathyroidism. *Am J Kidney Dis* 2000; **36:** 550–61.
17. Coburn JW, *et al.* Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. *Am J Kidney Dis* 2004; **43:** 877–90.
18. Dennis VC, Albertson GL. Doxercalciferol treatment of secondary hyperparathyroidism. *Ann Pharmacother* 2006; **40:** 1955–65.
19. Akiba T, *et al.* Controlled trial of falecalcitriol versus alfacalcidol in suppression of parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 1998; **32:** 238–46.
20. Akizawa T, *et al.* Long-term effect of 1,25-dihydroxy-22-oxavitamin D(3) on secondary hyperparathyroidism in haemodialysis patients: one-year administration study. *Nephrol Dial Transplant* 2002; **17** (suppl 10): 28–36.
21. Yasuda M, *et al.* Multicenter clinical trial of 22-oxa-1,25-dihydroxyvitamin D3 for chronic dialysis patients. *Am J Kidney Dis* 2003; **41** (suppl 1): S108–S111.
22. Doi S, *et al.* Effect of 22-oxacalcitriol on secondary hyperparathyroidism in hemodialysis patients. *Intern Med* 2003; **42:** 955–9.
23. Kubota M, *et al.* The effect of intraperitoneal 22-oxacalcitriol on secondary hyperparathyroidism in continuous ambulatory peritoneal dialysis patients (IPOX Study). *Adv Perit Dial* 2003; **19:** 227–30.
24. Murakami K, *et al.* Suppression of parathyroid hormone secretion in CAPD patients by intraperitoneal administration of maxacalcitol. *Clin Exp Nephrol* 2004; **8:** 134–8.
25. Hayashi M, *et al.* Comparison of the effects of calcitriol and maxacalcitol on secondary hyperparathyroidism in patients on chronic haemodialysis: a randomized prospective multicentre trial. *Nephrol Dial Transplant* 2004; **19:** 2067–73.
26. Palmer SC, *et al.* Meta-analysis: vitamin D compounds in chronic kidney disease. *Ann Intern Med* 2007; **147:** 840–53.
27. Grey A, *et al.* Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency. *J Clin Endocrinol Metab* 2005; **90:** 2122–6.

Hypoparathyroidism. Although parenteral calcium salts may be given acutely for hypocalcaemic tetany, long-term treatment of hypoparathyroidism (p.1087) usually aims at correction of associated hypocalcaemia with oral calcium salts and oral vitamin D compounds, which increase the intestinal absorption of calcium.

Hypoparathyroidism in *pregnancy* poses severe risks of fetal hyperparathyroidism with neonatal hypocalcaemic rickets, which may be fatal. Treatment with calcium and either colecalciferol or ergocalciferol in doses of 1.25 to 2.5 mg daily, or dihydrotachysterol 0.25 to 1.0 mg daily is essential.[1] Calcitriol, in doses of between 0.25 to 3 micrograms daily, with calcium supplementation, has also been suggested; the dosage is adjusted to physiological requirements during pregnancy.[2]

1. Hague WM. Treatment of endocrine diseases. *BMJ* 1987; **294:** 297–300.
2. Callies F, *et al.* Management of hypoparathyroidism during pregnancy - report of twelve cases. *Eur J Endocrinol* 1998; **139:** 284–9.

Inflammatory bowel disease. Some studies have found a high prevalence of vitamin D deficiency in patients with inflammatory bowel disease (IBD). The aetiology of this is not entirely clear and may be multifactorial.[1,2] Patients with IBD may have decreased exposure to sunlight since the incidence and prevalence of IBD are greatest in northern latitudes. Patients might also have inadequate dietary intake of vitamin D, since IBD patients may avoid foods, such as dairy products, that are generally fortified with this vitamin. Deficiency might also be due to malabsorption, especially in IBD patients that have undergone small-bowel resection, although intestinal absorption was normal in many IBD patients with low vitamin D concentrations. The use of drugs such as colestyramine, and disturbed enterohepatic circulation of vitamin D metabolites have also been proposed as mechanisms for hypovitaminosis D in patients with IBD, as has an increased loss of vitamin D through protein-losing enteropathy.[1,2] A study[3] in children and young adults with IBD also found a high prevalence of vitamin D deficiency in this patient population. Predisposing factors included dark-skinned complexion, winter season, lack of vitamin D supplementation, early stage of disease, more severe disease, and upper gastrointestinal tract involvement in patients with Crohn's disease. Vitamin D concentrations were positively correlated with serum albumin concentrations, leading the authors to conclude protein-losing enteropathy was a leading mechanism for deficiency. If this were so, both enteral and parenteral supplementation of vitamin D might prove inadequate at the usual dose, and in patients with active disease.

However, the American Gastroenterological Association concluded, in a review of osteoporosis in gastrointestinal diseases,[4] that osteomalacia and vitamin D deficiency were not common in IBD patients (including Crohn's disease) and were unlikely to be causes of most cases of diminished bone mineral density in patients with IBD.

1. Lim W-C, *et al.* Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2:** 308–15.
2. Pappa HM, *et al.* Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease.*Inflamm Bowel Dis* 2006; **12:** 1162–74.
3. Pappa HM, *et al.* Vitamin D status in children and young adults with inflammatory bowel disease. *Pediatrics* 2006; **118:** 1950–61.
4. Bernstein CN, *et al.* American Gastroenterological Association Clinical Practice Committee. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003; **124:** 795–841.

Malignant neoplasms. The active form of vitamin D, calcitriol (1,25-dihydroxycholecalciferol) has been found to promote tissue differentiation and to inhibit cellular proliferation *in vitro*. These findings have prompted investigation into the potential role and efficacy of vitamin D metabolites or analogues (sometimes referred to as deltanoids) in malignant neoplasms and in other disorders of cell growth such as psoriasis (see below).

There is laboratory evidence that vitamin D compounds can inhibit the growth of cancer cells, including those of the breast,[1,2] colon,[3] and prostate.[4,5] Epidemiological studies have suggested that vitamin D deficiency may be associated with higher risks of cancer.[6-9] Furthermore, increased sun exposure may be associated with improved survival for some cancers.[7,9] Phase I and II studies of calcitriol either alone, or with antineoplastics, have shown promising results.[10,11] A study in humans has been performed with the calcitriol derivative calcipotriol (p.1591); in this trial calcipotriol used topically in advanced or cutaneous metastatic breast cancer was considered to exert some positive effects and further investigation was considered warranted.[12] Regression of T-cell lymphoma of the skin (mycosis fungoides, p.657) has been reported after application of calcipotriol,[13] and after systemic treatment with calcitriol and a retinoid in a patient who failed to respond to topical calcipotriol.[14] However, 3 other patients with cutaneous T-cell lymphoma failed to respond to calcitriol and isotretinoin,[15] which may have been because of the phenotype or stage of the disease.[16] In a 7-year study in 36 282 postmenopausal women, of whom 18 176 received vitamin D_3 (400 units daily) and calcium, supplementation had no effect on the incidence of colorectal cancer.[17] This study has raised debate as to whether the dose of vitamin D used was insufficient.[7] A later analysis[18] of the study results suggested that supplementation had been of benefit in women in the placebo arms of the study but that this had been offset by an increase in risk in women also taking oestrogens. A smaller 4-year study[19] involving 1179 postmenopausal women given calcium with or without vitamin D_3 1100 units daily, or placebo, found that supplementation reduced all-cancer risk, and baseline and treatment-modified serum concentrations of vitamin D were strong predictors of cancer risk.

1. Colston KW, Hansen CM. Mechanisms implicated in the growth regulatory effects of vitamin D in breast cancer. *Endocr Relat Cancer* 2002; **9:** 45–59.
2. Cui Y, Rohan TE. Vitamin D, calcium, and breast cancer risk: a review. *Cancer Epidemiol Biomarkers Prev* 2006; **15:** 1427–37.
3. Kumagai T, *et al.* Vitamin D analog 19-nor-1,25-dihydroxyvitamin D : antitumor activity against leukaemia, myeloma, and colon cancer cells. *J Natl Cancer Inst* 2003; **95:** 896–905.
4. Chen TC, Holick MF. Vitamin D and prostate cancer prevention and treatment. *Trends Endocrinol Metab* 2003; **14:** 423–30.
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6. Garland CF, *et al.* The role of vitamin D in cancer prevention. *Am J Public Health* 2006; **96:** 252–61.
7. Schwartz GG, Skinner HG. Vitamin D status and cancer: new insights. *Curr Opin Clin Nutr Metab Care* 2007; **10:** 6–11.
8. Holick MF. Vitamin D: its role in cancer prevention and treatment. *Prog Biophys Mol Biol* 2006; **92:** 49–59.
9. Ingraham BA, *et al.* Molecular basis of the potential of vitamin D to prevent cancer. *Curr Med Res Opin* 2008; **24:** 139–49.
10. Trump DL, *et al.* Anti-tumor activity of calcitriol: pre-clinical and clinical studies. *J Steroid Biochem Mol Biol* 2004; **89–90:** 519–26.
11. Beer TM, Myrthue A. Calcitriol in cancer treatment: from the lab to the clinic. *Mol Cancer Ther* 2004; **3:** 373–81.
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14. French LE, *et al.* Remission of cutaneous T-cell lymphoma with combined calcitriol and acitretin. *Lancet* 1994; **344:** 686–7.
15. Thomsen K. Cutaneous T-cell lymphoma and calcitriol and isotretinoin treatment. *Lancet* 1995; **345:** 1583.
16. French LE, Saurat J-H. Treatment of cutaneous T-cell lymphoma by retinoids and calcitriol. *Lancet* 1995; **346:** 376–7.
17. Wactawski-Wende J, *et al.* Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006; **354:** 684–96. Correction. *ibid.*; 1102.
18. Ding EL, *et al.* Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women's Health Initiative randomized trial. *Int J Cancer* 2008; **122:** 1690–4.
19. Lappe JM, *et al.* Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007; **85:** 1586–91. Correction. *ibid.* 2008; **87:** 794.

Multiple sclerosis. Multiple sclerosis (p.892) is more common in regions further from the equator, and it has been suggested that sunlight exposure and vitamin D exert a protective effect. Studies have also found lower vitamin D concentrations in patients with multiple sclerosis. Results from two large prospective cohorts found an inverse relationship between intake of vitamin D from supplements and risk of the disease; no association was found between vitamin D intake from food and incidence of multiple sclerosis.[1] A prospective, case-control study[2] found that, among whites, the risk of multiple sclerosis significantly decreased with increasing concentrations of vitamin D; no significant association was found among blacks and Hispanics. However, the sample size in the latter groups were smaller and concentrations of vitamin D are lower among blacks. A review[3] found little evidence to support the effectiveness of vitamin D in the treatment of multiple sclerosis; although uncontrolled studies suggest vitamin D may be beneficial, small patient populations and confounding variables have limited the usefulness of the data.

1. Munger KL, *et al.* Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004; **62:** 60–65.
2. Munger KL, *et al.* Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; **296:** 2832–8.
3. Brown SJ. The role of vitamin D in multiple sclerosis. *Ann Pharmacother* 2006; **40:** 1158–61.

Osteomalacia and rickets. Treatment of osteomalacia and rickets (p.1084) primarily aims at correcting any underlying deficiency states, and vitamin D substances, calcium, or phosphate supplements may be given orally as necessary.

Where **rickets** is due to impaired synthesis of 1,25-dihydroxycholecalciferol (type I pseudodeficiency) or receptor resistance (type II pseudodeficiency) replacement therapy with calcitriol may be indicated (in the latter case with very high dose calcium),[1] while X-linked hypophosphataemic rickets is generally treated with phosphate supplementation and calcitriol.[2] The use of single large doses of a vitamin D substance (Stosstherapie), for the prophylaxis of rickets, is highly controversial because of problems with toxicity, although it may be effective in patients with rickets due to proven[3] or recalcitrant[4] vitamin D deficiency. Factors contributing to reported resurgences in rickets[2,4-8] include increased breast feeding without sufficient vitamin D supplementation, and less exposure to sunlight. A major risk factor for infants is maternal vitamin D deficiency (see Pregnancy and the Neonate, below). In the UK, the Department of Health advises that children aged 5 years and under be supplemented with 7 micrograms (280 units) daily,[8] but renewed public health campaigns have been called for, along with supplementation of infants from high-risk groups with 400 units of vitamin D daily.[6] Similar recommendations have been made in Australia and New Zealand.[4] In the USA, the American Academy of Pediatrics has recommended that all infants have a minimum intake of 200 units daily.[9] Others have commented that even 200 units daily may not be enough as a preventive measure,[2,10] and that, in those children with good exposure to sunlight, calcium supplementation may also be necessary.[11]

In adults, vitamin D deficiency may be asymptomatic. Most patients who present clinically do so because of muscle weakness,

or muscles aches and pains.[12] Even severe vitamin D deficiency may result in a syndrome of persistent, non-specific musculoskeletal pain, before the onset of the clinical presentation of **osteomalacia**.[13] However, others[14] have queried the association.

For discussion on doses of vitamin D considered sufficient for prophylaxis, see UK and US Recommended Dietary Intake, above; for treatment, see Uses and Administration, above. Because the process of ageing decreases the skin's ability to synthesise vitamin D, elderly people may be at risk of deficiency (see Administration in the Elderly, above).

1. Hochberg Z, *et al.* Calcium therapy for calcitriol-resistant rickets. *J Pediatr* 1992; **121:** 803–8.
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5. Kreiter SR, *et al.* Nutritional rickets in African American breast-fed infants. *J Pediatr* 2000; **137:** 153–7.
6. Shaw NJ, Pal BR. Vitamin D deficiency in UK Asian families: activating a new concern. *Arch Dis Child* 2002; **86:** 147–9.
7. Welch TR, *et al.* Vitamin D-deficient rickets: the reemergence of a once-conquered disease. *J Pediatr* 2000; **137:** 143–5.
8. Anonymous. Primary vitamin D deficiency in children. *Drug Ther Bull* 2006; **44:** 12–16.
9. Gartner LM, *et al.* Prevention of rickets and vitamin D deficiency: new guidelines for vitamin D intake. *Pediatrics* 2003; **111:** 908–10.
10. Greer FR. Vitamin D deficiency—it's more than rickets. *J Pediatr* 2003; **143:** 422–3.
11. Bishop N. Rickets today—children still need milk and sunshine. *N Engl J Med* 1999; **341:** 602–4.
12. Anonymous. Primary vitamin D deficiency in adults. *Drug Ther Bull* 2006; **44:** 25–9.
13. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 2003; **78:** 1463–70.
14. Block SR. Vitamin D deficiency is not associated with nonspecific musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Proc* 2004; **79:** 1585–6.

PREGNANCY AND THE NEONATE. It has been supposed that most infants receive adequate calcium and vitamin D during pregnancy and during breast feeding or bottle feeding to prevent the development of rickets. However, this has been disputed;[1,2] even infants born to vitamin D replete mothers become vitamin D deficient after 8 weeks if not supplemented, and those born to vitamin D deficient mothers will reach a deficient state more quickly. In many populations where sun exposure is severely limited and there is inadequate corrective vitamin D supplementation, there is also a high prevalence of vitamin D deficiency in nursing mothers.[3] It is accepted that there are certain groups of women whose infants may be at special risk of neonatal rickets; these include those suffering economic deprivation, those living at high latitudes, and Asian immigrants [i.e. from the Indian subcontinent] in northern Europe, especially in winter. It is therefore suggested that pregnant women in such circumstances should receive supplements as the diet and sunshine exposure may not be providing adequate calcium (1 to 1.2 g daily) or vitamin D (400 units daily).[4] Alternatively, 1000 units vitamin D daily during the third trimester, or a single dose of 100 000 to 200 000 units of ergocalciferol during the sixth or seventh month, has been proposed.[5] The Committee on Medical Aspects of Food Policy (COMA) in the UK recommended[6] in 1991 that pregnant women receive supplementary vitamin D to achieve an intake of 10 micrograms daily. However, a 2003 report commissioned by the NICE found insufficient evidence to assess the effectiveness of vitamin D in pregnancy and has recommended against routine vitamin D supplementation in healthy pregnant women.[7] A review[2] of dietary vitamin D requirements during pregnancy and lactation has stated that women who were vitamin D deficient at the beginning of their pregnancy remained deficient despite supplementation with 800 to 1600 units daily. The authors suggested that current recommendations in the UK and the USA were grossly inadequate during pregnancy, especially for ethnic minorities (see UK and US recommended dietary intake, above). Instead, they suggested that doses of about 2000 to 10 000 units daily would be needed in order to achieve normal vitamin D concentrations. Furthermore, routine vitamin D supplementation of infants in high-risk groups has been recommended (see Osteomalacia, above).

1. Welch TR, *et al.* Vitamin D-deficient rickets: the reemergence of a once-conquered disease. *J Pediatr* 2000; **137:** 143–5.
2. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr* 2004; **79:** 717–26.
3. Dawodu A, Wagner CL. Mother-child vitamin D deficiency: an international perspective. *Arch Dis Child* 2007; **92:** 737–40.
4. Misra R, Anderson DC. Providing the fetus with calcium. *BMJ* 1990; **300:** 1220–1.
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Osteopetrosis. For mention of the use of high-dose calcitriol in the management of osteopetrosis, see under Corticosteroids, p.1509.

Osteoporosis. Vitamin D concentrations have been found to correlate positively with bone mineral density (BMD),[1] and supplementation with vitamin D and calcium has led to beneficial increases in BMD in most trials.[2] Sufficient intake of vitamin D and calcium is recommended for prevention of osteoporosis (p.1084), and supplementation is an accepted baseline adjunctive treatment.[2,3] The age-related increase in fracture risk is influenced by BMD changes and an increased propensity to falls, attributable in part to a loss of muscular strength. In addition to its role in calcium homoeostasis, vitamin D status has also been correlated to muscular strength in older people.[3]

Studies using vitamin D (with or without calcium) for the prevention of fractures have produced conflicting results.[4-11] However, in elderly patients, in whom dietary deficiencies are common, calcium and vitamin D supplements are recommended (see Administration in the Elderly, above). Supplementation is also recommended in elderly institutionalised patients.[12] A meta-analysis[13] of fracture prevention trials found that oral vitamin D supplementation with between 700 to 800 units daily reduced the risk of hip and non-vertebral fractures in elderly patients. However, a systematic review[6] has stated that the effectiveness of vitamin D alone in fracture prevention remains unclear. Calcium may be necessary to optimise the clinical efficacy of vitamin D supplementation in terms of reducing fracture risk.[3] A meta-analysis[14] found that oral vitamin D appeared to reduce the risk of hip fractures only when calcium supplementation was added. However, another meta-analysis[15] found that the difference in relative risk reduction for all fracture types when vitamin D was added to calcium supplementation, was very small and statistically insignificant, although those with low vitamin D serum concentrations tended to have a greater risk reduction than those with normal vitamin D concentrations. A significant difference was seen between the effects of different vitamin D doses. While noting that this could be due to statistical artifact, the authors noted that their analysis had been limited by the scarcity of data for vitamin D doses higher than 800 units, and that it was possible that vitamin D would have a beneficial effect if the dose were greater than 800 units daily. It has been suggested[16] that the vitamin D analogues alfacalcidol and calcitriol are more effective for osteoporosis than ergocalciferol or colecalciferol. However, a systematic review[6] found no evidence of benefit for analogues compared with vitamin D.

Vitamin D is also recommended for the prevention of corticosteroid-induced osteoporosis (see Effects on Bones and Joints, p.1491).

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16. Ringe JD, Schacht E. Prevention and therapy of osteoporosis: the roles of plain vitamin D and alfacalcidol. *Rheumatol Int* 2004; **24:** 189–97.

Psoriasis. A vitamin D analogue, calcipotriol (p.1591), is often used as an alternative to more traditional topical drugs in the initial management of mild to moderate psoriasis (p.1583). Another vitamin D analogue, tacalcitol (p.1615), is used similarly. Initial studies with topical maxacalcitol,[1] falecalcitriol,[2] and paricalcitol[3] suggest they are safe and effective for psoriasis. Calcitriol itself has been tried, both topically[4-6] and orally.[7] Calcitriol ointment has been found to be as effective as calcipotriol ointment[8] and short-contact dithranol cream; skin irritation was less with calcitriol compared with dithranol.[9] While global improvement and severity scores were found to be better with betamethasone dipropionate ointment, remission times were longer with calcitriol treatment.[10]

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Renal osteodystrophy. See under Hyperparathyroidism, above.

Rheumatoid arthritis. A large cohort study[1] found an inverse correlation between vitamin D intake and the risk of developing rheumatoid arthritis. However, a small study[2] of serum vitamin D concentrations in patients with rheumatoid arthritis who had donated blood before the onset of symptoms, found no association between vitamin D deficiency and later development of rheumatoid arthritis, suggesting that vitamin D does not have an important role in the pathogenesis of rheumatoid arthritis.

1. Merlino LA, *et al.* Vitamin D intake is inversely associated with rheumatoid arthritis. *Arthritis Rheum* 2004; **50:** 72–7.
2. Nielen MMJ, *et al.* Vitamin D deficiency does not increase the risk of rheumatoid arthritis: comment on the article by Merlino et al. *Arthritis Rheum* 2006; **54:** 3719–20.

Rickets. See Osteomalacia and Rickets, above.

Preparations

BP 2008: Calcitriol Capsules; Calcium and Colecalciferol Tablets; Calcium and Ergocalciferol Tablets; Colecalciferol Injection; Colecalciferol Tablets; Ergocalciferol Injection; Ergocalciferol Tablets; Paediatric Vitamins A, C and D Oral Drops;
BPC 1973: Calcium with Vitamin D Tablets; Vitamins A and D Capsules;
USP 31: Calcifediol Capsules; Calcitriol Injection; Calcium with Vitamin D Tablets; Dihydrotachysterol Capsules; Dihydrotachysterol Oral Solution; Dihydrotachysterol Tablets; Ergocalciferol Capsules; Ergocalciferol Oral Solution; Ergocalciferol Tablets; Oleovitamin A and D; Oleovitamin A and D Capsules; Paricalcitol Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Aderosol; Alfa Calcimax†; Alpha D3; Dexiven; Findeclin Combi; Ostelin; Raquiferol; Rexamat†; Silcor†; Sterogyl; Vita D; ***Austral.:*** Calcijex; Citrihexal; Kosteo; Ostelin; Rocaltrol; Sitriol; Zemplar; ***Austria:*** AT 10; Bocatriol; Calcijex; Etalpha; Laevovit D ; Oleovit D ; Rocaltrol; Silkis; Vi-De ; Zemplar; ***Belg.:*** 1-Alpha; AT 10†; D-Cure; Dedrogyl; Rocaltrol; Silkis; ***Braz.:*** Alfad†; Calcijex; Innosfen; Ostriol†; Rocaltrol; Sigmacalcidol; Sigmatriol; Silkis; ***Canad.:*** Calcijex; D-Vi-Sol; Dnisdol; Hectorol; Hytakerol†; One-Alpha; Ostoforte; Riva D; Rocaltrol; Zemplar; ***Chile:*** Acuode; Alfa D†; Etalpha; Genevis D2†; Genevis†; Rocaltrol; Silkis; ***Cz.:*** Alpha D3; Calciferol; Calcijex; Infadin; OsteoD; Rocaltrol; Silkis; Tachystin; Vigantol; Zemplar; ***Denm.:*** Bocatriol; Dygratyl; Etalpha; Rocaltrol†; ***Fin.:*** Calcijex†; Deetipat; Devitol; Dygratyl; Etalpha; Jekovit; Silkis; Zemplar; ***Fr.:*** Adrigyl†; Dedrogyl; Densical vitamine D ; Rocaltrol; Silkis; Sterogyl; Un-Alfa; Uvedose; Uvesterol D; Zyma-D2†; Zymad; ***Ger.:*** AT 10; Bocatriol; Bondiol; D Vicotrat; Decostriol; Dedrei; Dedrogyl; Dekristol; Doss; EinsAlpha; Ospur D ; Osteotriol; Rocaltrol; Silkis; Tachystin; Vigantol; Vigantoletten; Zemplar; ***Gr.:*** A-Calcid; A-Ostin-D3; Abbocalcijex; Alcidolin; Alestopor; Alfacalcil; Alfadel; Alpha D3; Alpha-Due; Alpha-Plus; Alphabikal; Alphacal; Alphasidol; Alphazol; Antebe; Axelanol; Baludol; Biovit; Calcidrops; Calcodol-D3; Calfadol; Calinol; Caltrioject; D-Triol; Dedrogyl; Didrogyl; Emarfen; Helposteol; Iasvest; Lifercal; Losefan; Mega-Alpha; One-Alpha; Ossidrol; Ostelin; Osteovile; Ostitriol; Otari; Silkis; Sterogyl; V-D-Bone; Vitocalcit; Votrace; Zemplar; ***Hong Kong:*** Alpha D3; Bon-One; Calcijex; Decostriol; One-Alpha; Rocaltrol; Silkis; Zemplar; ***Hung.:*** Alpha D3; AT 10†; Calcijex; Laevovit D †; Osteo D; Rocaltrol; Silkis; Tachystin; Vigantol; Zemplar; ***India:*** Alfacip; Alpha D3; Alphadol; Arachitol; Aristrol†; Calcirol; Minroset; Rolsical; ***Indon.:*** Bon-One; Calcijex; Calcit; Ecatrol; One-Alpha; Oscal; Osteofem; Ostovell; Ostriol; Ro-

The symbol † denotes a preparation no longer actively marketed

caltrol; ***Irl.:*** Calcijex†; One-Alpha; Rocaltrol; Silkis; Zemplar; ***Israel:*** Alpha D3; Calcijex; One-Alpha; ***Ital.:*** Alpha D3; Atiten; Calcijex; Dediol; Deril; Dibase; Didrogyl; Difix; Diseon; Diserinal; Geniad; Ostelin; Ostidil-D3; Rocaltrol; Sefal; Silkis; Tridelta; Trikal; Zemplar; ***Jpn:*** Alfarol; Hornel; Onealfa; Oxarol; Rocaltrol; ***Malaysia:*** Calcijex; Fairy ADE; One-Alpha; Osteocap; Rocaltrol; Roical; Zemplar; ***Mex.:*** Alfad; Altrical; Altrol; Calciofem; Geldex; Lemytriol; Rocaltrol; Silkis; Tirocal; Zemplar; Zygium; ***Neth.:*** Calcijex; Devaron; Dihydral; Etalpha; Rocaltrol; Silkis; Zemplar; ***Norw.:*** AFI-D ; Calcijex; Etalpha; Rocaltrol; Silkis; Zemplar; ***NZ:*** CalD; One-Alpha; Rocaltrol; ***Philipp.:*** Bon-One; Osteomeg; Rocaltrol; Silkis; ***Pol.:*** Alfadiol; Calcijex; Devikap; Devisol; Juvit D ; Kalcytriol; Rocaltrol; Silkis; Vigantol; Vigantoletten; ***Port.:*** Calcijex; Dedrogyl; Etalpha; Rocaltrol; Silkis; Vigantol; Zemplar; ***Rus.:*** Alpha D3 (Альфа Д3-тев); Aquadetrim (Аквадетрим); Etalpha (Этальфа); Osteotriol (Остеотриол)†; Tachystin (Тахистин); Vigantol (Вигантол); ***S.Afr.:*** AT 10; One-Alpha; Rocaltrol; ***Singapore:*** Alpha D3; Bon-One; Bongreen†; Calcijex; One-Alpha; Rocaltrol†; Roical; Silkis; Zemplar; ***Spain:*** Calcijex; Etalpha; Hidroferol; Oseofort; Rocaltrol; Silkis; Zemplar; ***Swed.:*** Calcijex; Devitre†; Dygratyl; Etalpha; Rocaltrol; Zemplar; ***Switz.:*** AT 10; Bocatriol†; Calcijex; Rocaltrol; Silkis; Vi-De ; Zemplar; ***Thai.:*** Alpha D3; Bon-One; Calcit; Decostriol; Meditrol; One-Alpha; OsteoD; Rocaltrol; ***Turk.:*** Alpha D3; Calcijex; Devit-3; One-Alpha; Osteo-D; Rocaltrol; ***UK:*** AT 10; Calcijex; One-Alpha; Rocaltrol; Silkis; Zemplar; ***USA:*** Calciferol; Calcijex; Calderol; Delta-D; DHT; Drisdol; Hectorol; Hytakerol†; Maximum D3; Rocaltrol; Zemplar; ***Venez.:*** Alpha D3; Rocaltrol; Silkis; Zemplar.

Multi-ingredient: ***Arg.:*** A-D-C; AD Shock; Adermicina; Anartrit; Atomoderma A-D; Calcimax D3; Calcimax Magnesio; Calcio Cit; Calcio Masticable; Calcional D3; Calcium D†; Calnier-D; Caltrate + D; Cavirox; Cavirox Cit; Citramar D; Dermosan; Dr Selby; Femorel Max; Fosamax Plus; Full Calcio; Glossderm†; Magnesio Incaico; Ostram D3; Regenesis Max; Regucal D; Ribastamin Duo; Sinamida Cicatrizante†; Snella; Taxus; Ultracalcium D3; Vitapelen†; ***Austral.:*** Bio Magnesium; Caltrate + Vitamin D; Caltrate Plus; FAB Tri-Cal; Fosamax Plus; Prosteo†; Soy Forte with Black Cohosh†; ***Austria:*** Cacit mit Vitamin D ; Cal-D-or; Cal-D-Vita; Cal-De; Calcichew D ; Calcimagon-D3; Calcipot D ; Calcisan D; Calcium Plus; Calcium-D-Sandoz; Kombi-Kalz; Maxi-Kalz Vit D3; Oleovit A + D; Ruticalzon; ***Belg.:*** Cacit Vitamine D ; D-Vital; Fosavance; Newderm†; Sandoz Ca-D; Steovit D3; Topcal D3†; ***Braz.:*** AD-Til; ADE 2 (Adedois); Adecal; Adederme; Adeforte; Aderogil D3; Alendil Calcio D; Babymed; Calcifix B12; Calcifix Irradiado; Calcinol Complexo; Calcium D3; Calde; Caltrate + D; Caltrate + M; Caridem†; Dermalisan; Dermoden; Gaduol†; Glossaliv; Hipoderme; Hipodermon; Hipodex; Hipoglos; Maxicalc-D; Miocalven D; Multiderme; Natecal D†; Os-Cal + D; Ossocal-D; OsteoNutri; Pronenen; Reposcal D; Sensibaby; Solemil†; Suavederm; Vitadesan; ***Canad.:*** A & D; A & D Ointment†; Antiseptic Skin Cream†; Cal D; Calburst†; Calcia; Calcite D; Calcium D; Calcium Magnesium Plus†; Caltrate Plus; Caltrate Select; Caltrate with Vitamin D; Mega Cal Calcium†; Neo Cal D; Nu Cal D; Nutrol A D; Os-Cal D; Viactiv; ***Chile:*** Aplical-D†; Brexon†; Cadevit; Calcefor D; Calcigran; Calcigran D; Calcimax D3; Calcio Day D†; Calcio Nil Forte†; Calciovit Puro; Calcium Forte D; Calcium-Sandoz + D; Calcium-Sandoz Forte D; Calcivorin D; Caldar-D; Caldeval; Caprimida D; Caprimida D Balance; Crevet Calcio + D3 + C; Dermaglos Plus†; Dical-D†; Elcal-D; Kaplus-D; Levucal D; Macrocal-D; Natecal D; Nenegloss; Oseofort; Osteocaps; Ostram D3; Pediaderm†; Platsul A; Pomada Vitaminica; Povin; Sanidecal-D; Sanoderm; Trical-D; ***Cz.:*** Adrovance; Calcichew D ; Caltrate Plus; Fosavance; Ideos; Infadolan; Kombi-Kalz; Osteocare; Vita-Calc†; Vitacalcin D†; ***Denm.:*** Calcichew D ; CaviD; Ideos†; ***Fin.:*** Calcichew D ; D-Calsor; Fosavance; Ideos; Kalcipos-D; Ostram-Vit D †; ***Fr.:*** Actonelcombi; Adrovance; Arthrolib; Cacit Vitamine D ; Calcidose Vitamine D; Calciforte Vitamin D ; Calciprat D ; Calcos Vitamine D ; Calperos D ; Caltrate Vitamine D ; Eptavit; Estrofort; Fixical Vitamine D ; Fluosterol; Fosavance; Frubiose Vitamine D†; Ideos; Metocalcium; Osseans D3; Osteocal D3; Ostram Vitamine D ; Zymaduo; ***Ger.:*** CalciAPS D3; Calcigen D; Calcilac KT; Calcimagon-D3; Calcimed D ; Calcium D ; Calcium Verla D; Calcium-D-Sandoz†; Calcium-dura Vit D ; Calcium-Sandoz D Osteo; Calcivit D; calcivitase†; D-Fluoretten; Fluor-Vigantoletten; Fosavance; Frubiase Calcium forte 500; Ideos; Ossofortin D; Ossofortin forte; Ossofortin Plus; Ossofortin†; Ossplusvit D ; Ossplusvit S†; Osteoplus; Ostocavid; Remicalcin + D ; Sandocal-D; Strafortin†; Zymafluor D; ***Gr.:*** Adrovance; Aquasol A+D; Cal+D; Calcidina; Calcioral D3; Calcium-D-Sandoz; Cald 3-Therapy; Caldesil; Calvidin; D-Calcium; Decal; Dioflam; Flavobion-C; Fosavance; Ideos; Natecal D3; Taminol; Videcalcio; ***Hong Kong:*** Calcichew D †; Calcioday-D; Calperos D ; Caltrate + D; Caltrate + Soy; Caltrate Plus; Citracal + D; Doctor's Choice Fortified Bone Support; Flavettes Cal D3; Fosamax Plus; Mega-Cal with Vit D; Os-Cal + D; Osteocare; ***Hung.:*** Actonel Trio; Calcichew D ; Calcisedron-D; Calcium-D-Sandoz; Calcivid; Caldea†; Fosavance; Ideos; Neogranormon; Osteocare; Vitacalc†; ***India:*** Alfacip Plus; Anemidox; Aristrol Forte†; Cafe-Kit†; Cal-Aid; Calcigen; Calcinol; Calcom; Calfa-Plus; Calmix†; Cipcal; Cipcal M; Incad; Kalzana; Kemicetine Antiozena; Logical; Macalvit; Milical; Milical-XP†; Minroset-C; Omilcal; Ossivite; Ostebon; Osteobon; Osteobon-M; Ostocalcium; Ostocalcium B-12; Sandocal with Vit D ; Sharkomalt; Sharkovit; Sigmacalvit; Styptocid; Trical-D; ***Indon.:*** Cal-95; Calc-Os; Calcidin; Calosbon; Calporosis D; Calsical; Cavit D3; CDR Fortos; Day-Cal; Dumocalcin Plus; Epocaldi; Fosamax Plus; Hi-Bone; Hical; Jointfit; Licokalk Plus; Menoxa; Osfit; Ossovit; Osteocal Plus; Osteocare; Osteopor; Scott's E Vita; Steopor; Vitacal-D; ***Irl.:*** Bio-Calcium + D ; Bio-Calcium + D + K; Calcichew D ; Calvidin; Chocovite; Decal; Fosavance; Ideos; Osteofos D3; ***Israel:*** Aquitol†; Baby A + D; Calcichew D ; Calcium Citrate; Caltrate + Vit D; Oleovit A + D †; Vitamidyne A and D; ***Ital.:*** AD Pabyrn; Adisterolo; Biocalcium D3; Cacit Vitamina D3; Cadtre; Calcicold3; Calcidon; Calciozim†; Calcium-D3-Sandoz; Calciumcafe; Calisvit; Calma D3; CalplusD3; Caltrate; Carbo D3; Cartago; Dicalcium†; Ditrevit; Ditrost; Effercal D3; Eurocal D3; Fitogen; Fosavance; Foscald3; Granoleina†; Ideos; Kalaz D3; Metocal Vitamina D; Natecal; Orotre; Osteofos D3; Ostram D ; Tonacal D3; Urtotre; ***Malaysia:*** Adult Citrex Cal-Mag-D3; Bio-Enhanced Calcium Plus; Calcioday-D†; Caltrate + D; Caltrate Plus; Citracal + D†; Dumocalcin†; Effcal; Fosamax Plus; Junior Citrex Cal-Mag-D3; Milical; Os-Cal + D†; Revital Calcium D3; Vitacal + D†; ***Mex.:*** Adekals; Adekon; Adekon C; Adeloren†; Adibal; Alfem; Aquasol AD; Caltrate + D; Caltrate + M; Caltrate + S; Caltrec†; Capent; Dical; Fosamax Plus; Minerbon; Os-Cal + D; Osteocalcio; Osteomin D; Posture D; Sandoz Calcium + D; Sutin†; Valmetrol-3; Vidamil; Vitalorange; ***Neth.:*** CaD; Calci-Chew D3; Calisvit; Halitran; Ideos; Sandoz Ca-D; ***Norw.:*** Calcigran; Ideos; Nycoplus Calcigran; ***NZ:*** Fosamax Plus; ***Philipp.:*** Agre-Calvit; Calciday; Caltrate Plus; Calvit; Esvical; Fosavance; Her Soy Plus; Osteo-4; Osteo-D; Osteocare; Vandol; ***Pol.:*** Alantavit; Calcium 500D; Caldetrin; Caltrate + Witamina D; Caltrate Plus; Ideos; Orocal D ; Ostowap D ; Tranvit; Vicalvit D; ***Port.:*** Bidiam; Cacit; Calcigenol; Calcior-D; Calcitab D; Calcium 600†; Calcium D; Calcium-D-Sandoz; Caltrate Plus Mastigavel†; Caltrate Plus†; Decalcit; Densical D; Dermabut; Fosavance; Ideos; Natecal D; Ostram D3†; Osvical; ***Rus.:*** Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Calcium-D3 Nycomed (Кальций-Д3 Никомед); Ideos (Идеос); Natecal D (Натекаль Д); Vectrum Calcium (Вектрум Кальций); ***S.Afr.:*** Phytopause BSF; Vandol†; ***Singapore:*** BoneCare; Cal-D3†; Calcioday-D†; Calcium-D; Caltrate + Soy; Caltrate + Vit D; Caltrate Plus; Cavit-D3; Citracal + D; Dumocalcin; Effcal; Fosamax Plus; Glucocal; Os-Cal + D; Vitacal; Vitacal + D; ***Spain:*** Adiod; Biominol A D; Calcial D; Calcio 20 Complex; Calcio 20 Fuerte; Calcio D; Calcium-Sandoz Forte D; Caosina D; Carbocal D; Cicatral; Cimascal D; Creacal†; Disnal; Fosavance; Grietalgen; Grietalgen Hidrocort†; Ibercal D; Ideos; Mastical D; Maxbon; Mencalisvit; Metafisol; Mitosyl; Natecal D; Osteomerck; Ostine; Osvical D; Redoxon Calcivit; Tepox Cal D; Trabex; Veriscal D; ***Swed.:*** AD-vitamin; Cal-D-Vita; Calcichew D ; Ideos; Kalcipos-D; ***Switz.:*** Cal-De†; Calcimagon-D3; Calcium D Sauter; Calcium-Sandoz D3; Calcivit; Calperos D ; Decalcit; Malvedrin; Osteocal D3; Phytopharma Calcium; Riccovitan†; ***Thai.:*** Bio-Calcium + D3 + K; Cal-D-Vita; Calcalcin; Calcioday-D†; Calcium D; Caldoxon; Caltab W/Vitamin D; Caltrate + D; Caltrate Plus; Calvin Plus; Combi-Cal†; Effcal; Fortica; Ostone-B12; Prima-Cal Plus Vit D; ***Turk.:*** Balya; Cal-D-Vita; Calcidine; Calcimax D3; Calcium-D-Sandoz; Caltrate; D-Flor; Folic Plus; Fosfokalsiyum; Kalsifluor; Nature Made Oyster Shell Calcium; Osteocare; ***UK:*** Actonel Combi; Adcal-D ; Cacit D3; Calceos; Calcichew D ; Calcium and Ergocalciferol Tablets; Calfovit D3; Caltrate Plus; Crampex; Fosavance; Haliborange Calcium Plus Vitamin D; Natecal D3; Osteo-Life; Osteocare; S.P.H.P.; ***USA:*** A and D Medicated; Calcarb with Vitamin D; Calcet; Calcium 600 + D; Calel-D; Caltrate + Iron & Vitamin D; Caltrate + Vitamin D; Caltrate Plus; Calvite P & D; Citracal + D; Citracal Creamy Bites†; Citracal Plus with Magnesium; Clocream; Desert Pure Calcium; Diaper Guard; Fosamax Plus; Fosteum; Lobana Derm-Aide; Lobana Peri-Garde; Os-Cal + D; Oyster Calcium with Vitamin D; Paladin; Posture-D; ***Venez.:*** A-D-Vit; Adaderm; Adenar; Brocalcio D3; Cal.Cell; Calcibon D; Calcibon D Magnesio; Calcibon D Soya; Calcibon Natal; Calcinor D; Calcio Ostelin; Calciofar D; Calciogenol; Calcion D Plus; Calcitrex D3; Calpal D†; Caltrate + D; Citracal D; Dicalcico†; Hipoglos†; Ideos; Kidcal; Maltocalcine; Oscal D; Vandol; Viteno†.

Vitamin E Substances

Vitamina E.

ATC — A11HA03.

ATC Vet — QA11HA03.

NOTE. The food additive number E306 is used for tocopherols.

Vitamin E is a generic term applied to a large number of natural or synthetic compounds. The most important substances are the **tocopherols** of which **alpha tocopherols** are the most active and widely distributed in nature; other naturally occurring tocopherols include beta, gamma, and delta tocopherols, but these are not used in therapeutics. The other group of compounds with vitamin E activity are the tocotrienols.

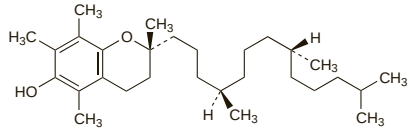
Alpha tocopherols occur naturally in the *d* optical isomer form, which is more active than the synthetic racemic *dl* form; for further details concerning the comparative activities of the different forms and isomers of vitamin E compounds, see under Units, below.

d-Alpha Tocopherol

d-Alfa Tokoferol; (+)-Alpha-Tocopherol; *RRR*-alpha-Tocophérol; *RRR*-alpha-Tocopherolum; Natural Alpha Tocopherol; Natural α-Tocopherol; RRR-α-Tocopherolum; RRR-α-Tokoferol; D-α-Tocoferol; *RRR*-α-Tocopherol; *d*-α-Tocopherol; *RRR*-α-tocopherolum; *RRR*-α-tokoferol; *RRR*-α-Tokoferoli; *RRR*-α-Tokoferolis. (+)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol.

$C_{29}H_{50}O_2$ = 430.7.

CAS — 59-02-9.



Pharmacopoeias. In *Eur.* (see p.vii). *US* allows it under the title Vitamin E.

Ph. Eur. 6.2 (*RRR*-α-Tocopherol; *RRR*-Alpha-Tocopherol BP 2008). A clear, colourless, or yellowish-brown viscous oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in fatty oils. Store under an inert gas in airtight containers. Protect from light.

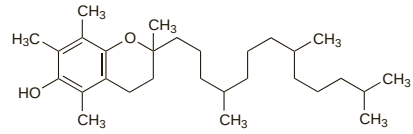
USP 31 (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is unstable to air and light, particularly in alkaline media. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store under an inert gas in airtight containers. Protect from light.

dl-Alpha Tocopherol

all-rac-α-Tokoferol; all-*rac*-α-Tocopherol; Alpha Tocopherol; (±)-Alpha-Tocopherol; E307; int-rac-α-Tocopherolum; int-*rac*-α-Tocopherol; Synthetic Alpha Tocopherol; Synthetic α-Tocopherol; DL-α-Tocoferol; Tocoferolum Alfa; α-Tocopherol; *dl*-α-Tocopherol; α-Tocopherolum; α-Tokoferol; Tokoferol-alfa; tout-*rac*-α-Tocophérol; Visų racematų α-Tokoferolis. (±)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol.

$C_{29}H_{50}O_2$ = 430.7.

CAS — 10191-41-0.



Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn. US* allows it under the title Vitamin E.

Ph. Eur. 6.2 (all-*rac*-α-Tocopherol; all-*rac*-Alpha Tocopherol BP 2008). A clear, colourless or yellowish-brown viscous oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in fatty oils. Store under an inert gas. Protect from light.

USP 31 (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is unstable to air and light, particularly in alkaline media. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store under an inert gas in airtight containers. Protect from light.

d-Alpha Tocoferil Acetate

d-Alpha Tocopheryl Acetate; (+)-Alpha-Tocopherol Acetate; (+)-Alpha-Tocopheryl Acetate; *RRR*-alpha-Tocophéryle, acétate de; *RRR*-alpha-Tocopherylis acetas; RRR-α-Tocopherylis acetas; RRR-α-Tokoferylu octan; D-α-Tocoferilo, acetato de; Tocoferoli Alfa *RRR* Acetas; *RRR*-α-Tocopheroli Acetas; *d*-α-Tocopheryl Acetate; *RRR*-α-Tocopheryl Acetate; *RRR*-α-Tocopherylis Acetas; *RRR*-α-Tokoferilio acetatas; *RRR*-α-Tokoferol-acetát; Tokoferol-acetát alfa *RRR*; Tokoferol-alfa-*RRR*-acetát; *RRR*-α-Tokoferylacetat; *RRR*-α-Tokoferyyliasetaatti. (+)-α-Tocopherol acetate.

$C_{31}H_{52}O_3$ = 472.7.

CAS — 58-95-7.

Pharmacopoeias. In *Eur.* (see p.vii). *US* allows it under the title Vitamin E.

Ph. Eur. 6.2 (*RRR*-α-Tocopheryl Acetate; *RRR*-Alpha-Tocopheryl Acetate BP 2008). A clear, colourless or slightly greenish-yellow, viscous oily liquid. Practically insoluble in water; soluble in alcohol; freely soluble in dehydrated alcohol, in acetone, and in fatty oils. Protect from light.

USP 31 (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It may solidify in the cold. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store in airtight containers. Protect from light.

dl-Alpha Tocoferil Acetate

dl-Alfa Tokoferil Asetat; all-rac-α-Tokoferylu octan; all-*rac*-α-Tocopheryl Acetate; Alpha Tocopheryl Acetate; *dl*-Alpha Tocopheryl Acetate; (±)-Alpha-Tocopherol acetate; int-rac-α-Tocopherylis acetas; int-*rac*-α-Tocopherylis Acetas; DL-α-Tocoferilo, acetato de; Tocoferoli Alfa Acetas; α-Tocopherol Acetate; α-Tocopheroli Acetas; *dl*-α-Tocopheryl Acetate; Tokoferol alfa-acetát; Tokoferolu octan; tout-*rac*-α-Tocophéryle, acétate de; Visų racematų α-Tokoferilio acetatas. (±)-α-Tocopherol acetate.

$C_{31}H_{52}O_3$ = 472.7.

CAS — 7695-91-2; 52225-20-4.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn. US* allows it under the title Vitamin E.

Eur. also has a monograph for the concentrated powdered form.

Ph. Eur. 6.2 (all-*rac*-α-Tocopheryl Acetate; all-*rac*-Alpha Tocopheryl Acetate BP 2008). A clear, colourless or slightly greenish-yellow, viscous, oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, and in fatty oils. Protect from light.

Ph. Eur. 6.2 (α-Tocopheryl Acetate Concentrate (Powder Form); α-Tocopherylis Acetatis Pulvis; Alpha Tocopheryl Acetate Concentrate (Powder Form) BP 2008). It is prepared either by finely dispersing *dl*-alpha tocoferil acetate in a suitable carrier (e.g. gelatin, acacia, carbohydrates, lactoproteins, or a mixture of these) or by adsorbing *dl*-alpha tocoferil acetate on to silicic acid. The concentrate contains not less than 25% of *dl*-alpha tocoferil acetate. Almost white, yellowish, or light-brown small particles. Depending on the formulation, the powder may be practically insoluble in water or may swell or form a dispersion. Store in well-filled airtight containers. Protect from light.

USP 31 (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store in airtight containers. Protect from light.