d-Alpha Tocoferil Acid Succinate

d-Alpha Tocopheryl Acid Succinate; *d*-Alpha-Tocopherol acid succinate; *RRR*-alpha-Tocophéryle, hydrogénosuccinate de; *RRR*-alpha-Tocopherylis hydrogenosuccinas; D-α-Tocoferilo, succinato ácido; Tocoferoli Alfa *RRR* Hydrogenosuccinas; *RRR*-α-Tocoferoli Hydrogenosuccinas; *d*-α-Tocopheryl Acid Succinate; *RRR*-α-Tocopheryl Hydrogen Succinate; *RRR*-α-Tocopherylis Hydrogenosuccinas; *RRR*-α-Tokoferilio-vandenilio sukcinatas; Tokoferol-alfa-*RRR*-hydrogen-sukcinát; *RRR*-α-Tokoferol-hidrogén-szukcinát; *RRR*-α-Tokoferylvätesuccinat; *RRR*-α-Tokoferyylivetysuksinaatti. (+)-α-Tocopherol hydrogen succinate.

$C_{33}H_{54}O_5$ = 530.8.

CAS — 4345-03-3.

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

US also includes Vitamin E Polyethylene Glycol Succinate, a mixture formed by the esterification of *d*-alpha tocoferil acid succinate with a macrogol.

Ph. Eur. 6.2 (*RRR*-α-Tocopheryl Hydrogen Succinate; *RRR*-Alpha Tocopheryl Hydrogen Succinate BP 2008). A white or almost white crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol and in acetone; very soluble in dichloromethane. Protect from light.

USP 31 (Vitamin E). A white, practically odourless, powder. M.p. about 75°; it is unstable when held molten. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol, in acetone, in ether, and in vegetable oils; very soluble in chloroform; slightly soluble in alkaline solution. Store in airtight containers. Protect from light.

dl-Alpha Tocoferil Acid Succinate

dl-Alpha Tocopheryl Acid Succinate; Alpha Tocopheryl Hydrogen Succinate; DL-alpha-Tocophéryle, hydrogénosuccinate de; DL-alpha-Tocopherylis hydrogenosuccinas; DL-α-Tocoferilo, succinato ácido; Tocoferoli Alfa Hydrogenosuccinas; DL-α-Tocopheroli Hydrogenosuccinas; *dl*-α-Tocopheryl Acid Succinate; DL-α-Tocopheryl Hydrogen Succinate; DL-α-tocopherylis Hydrogenosuccinas; DL-α-Tokoferilio-vandenilio sukcinatas; Tokoferol-alfa hydrogen sukcinát; DL-α-tokoferol-hidrogén-szukcinát; DL-α-Tokoferylvätesuccinat; DL-α-Tokoferyylivetysuksinaatti. (±)-α-Tocopherol hydrogen succinate.

$C_{33}H_{54}O_5$ = 530.8.

CAS — 17407-37-3.

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

Ph. Eur. 6.2 (DL-α-Tocopheryl Hydrogen Succinate; Alpha Tocopheryl Hydrogen Succinate BP 2008). A white or almost white, crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol and in acetone; very soluble in dichloromethane. Protect from light.

USP 31 (Vitamin E). A white, practically odourless, powder. M.p. about 70°; it is unstable when held molten. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol, in acetone, in ether, and in vegetable oils; very soluble in chloroform; slightly soluble in alkaline solution. Store in airtight containers. Protect from light.

Units

Though the potency of preparations of vitamin E is still sometimes expressed in units, the International Standard for vitamin E was discontinued in 1956. The International Unit was the activity contained in 1 mg of a standard preparation of *dl*-alpha-tocoferil acetate. Past editions of the USP have stated that in expressing vitamin E activity of tocopherol products, the following equivalents of 1 mg were to be used:

- *d*-alpha tocopherol, 1.49 units
- *dl*-alpha tocopherol, 1.1 units
- *d*-alpha tocoferil acetate, 1.36 units
- *dl*-alpha tocoferil acetate, 1 unit
- *d*-alpha tocoferil acid succinate, 1.21 units
- *dl*-alpha tocoferil acid succinate, 0.89 unit.

For dietary purposes, vitamin-E activity may now be expressed in terms of alpha tocopherol equivalents (α-TEs). One α-TE is the activity contained in:

- 1 mg of *d*-alpha tocopherol (natural alpha tocopherol; *RRR*-α-tocopherol)
- 1.4 mg *dl*-alpha tocopherol
- 1.1 mg *d*-alpha tocoferil acetate
- 1.5 mg *dl*-alpha tocoferil acetate
- 1.2 mg *d*-alpha tocoferil acid succinate
- 1.7 mg *dl*-alpha tocoferil acid succinate.

Adverse Effects and Precautions

Vitamin E is usually well tolerated. Large doses may cause diarrhoea, abdominal pain, and other gastrointestinal disturbances, and have also been reported to cause blurred vision, dizziness, fatigue and weakness. Contact dermatitis has occurred after topical application.

Large doses of vitamin E have been reported to increase bleeding tendency in vitamin-K deficient patients such as those taking oral anticoagulants. However, it has also been suggested that it may increase the risk of thrombosis in some patients, such as those taking oestrogens. The clinical significance of these effects is not known.

A higher incidence of necrotising enterocolitis has been noted in premature infants weighing less than 1.5 kg treated with vitamin E.

Carcinogenicity. For mention of an *increased* incidence of second primary cancers and reduced cancer-free survival in patients with head and neck cancer receiving vitamin E (and betacarotene initially), see Prophylaxis of Malignant Neoplasms, p.1927.

Effects on mortality. While some studies of antoxidants, including vitamin E, have suggested beneficial effects on the progression of cardiovascular disease and cancer, other studies (including large randomised studies such as the Women's Health Study[1]) have shown little or no effect.[2] Vitamin E may even cause an increased risk of heart failure, or incidence of cancer (see Prophylaxis of Ischaemic Heart Disease, p.1926, and Prophylaxis of Malignant Neoplasms, p.1927). A meta-analysis[3] and a systematic review[4] of vitamin E supplementation found no benefit in terms of mortality. Another meta-analysis[5] found no effect for vitamin E supplementation on all-cause mortality overall. However, in dose-response analysis, high-dosage vitamin E (greater than 400 units daily) showed a significantly increased risk; there was some suggestion of a decreased risk with low doses (less than 400 units daily); all-cause mortality progressively increased for doses greater than 150 units daily. (Such an effect was not seen in the Women's Health Study, in which participants received 600 units on alternate days.) Some have commented[6] that the meta-analysis may not have isolated the effects of vitamin E, since in many of the trials studied, other nutritional supplements had been given, including betacarotene, itself possibly associated with an increased risk of death; however, the use of high-dose vitamin E was considered unjustified. A systematic review of antoxidant supplementation found that vitamin E, either singly or with other antoxidants, increased mortality.[7] A large cohort study in a population aged 65 years or older, after adjustment for age and sex, found that there was no association between vitamin E use and mortality. However, mortality was increased in vitamin E users who had a history of cardiovascular disease, or who were taking nitrates, warfarin, and diuretics. There was a consistent trend towards reduced mortality in vitamin E users without cardiovascular disease or taking these drugs. The authors concluded that vitamin E should be used with caution in those with cardiovascular disease, and that further investigation of the potential interaction between vitamin E and particular drugs was warranted.[8]

1. Lee I-M, *et al.* Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005; **294:** 56–65.
2. Brown BG, Crowley J. Is there any hope for vitamin E? *JAMA* 2005; **293:** 1387–90.
3. Vivekananthan DP, *et al.* Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003; **361:** 2017–23.
4. Shekelle PG, *et al.* Effect of supplemental vitamin E for the prevention and treatment of cardiovascular disease. *J Gen Intern Med* 2004; **19:** 380–9.
5. Miller ER, *et al.* Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; **142:** 37–46.
6. Greenberg ER. Vitamin E supplements: good in theory, but is the theory good? *Ann Intern Med* 2005; **142:** 75–6.
7. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).
8. Hayden KM, *et al.* Cache County Investigators. Risk of mortality with vitamin E supplements: the Cache County study. *Am J Med* 2007; **120:** 180–4.

Neonatal toxicity. For a review and discussion of liver and kidney toxicity in premature neonates associated with an intravenous preparation of vitamin E (E-Ferol) and attributed to the inclusion of polysorbates, see Effects in Infants, p.1919.

Interactions

Various drugs may interfere with the absorption of vitamin E including colestyramine, colestipol, and orlistat. High doses of vitamin E may increase the effects of oral anticoagulants.

Pharmacokinetics

Absorption of vitamin E from the gastrointestinal tract is dependent on the presence of bile and on normal pancreatic function. The amount of vitamin E absorbed varies widely between about 20% and 80% and appears to decrease as the dose is increased. It enters the blood via the chylomicrons in the lymph and is bound to beta lipoproteins. It is widely distributed to all tissues, and stored in adipose tissue. Some vitamin E is metabolised in the liver to glucuronides of tocopheronic acid and its γ-lactone. Some is excreted in the urine, but most of a dose is slowly excreted in the bile. Vitamin E appears in breast milk but is poorly transferred across the placenta.

Human Requirements

The daily requirement of vitamin E has not been clearly defined but is probably about 3 to 12 mg of *d*-alpha tocopherol or the equivalent of other vitamin E substances. Requirements increase with increased dietary amounts of polyunsaturated fatty acids. There appears to be no evidence that supplements are required in subjects on balanced diets.

Vitamin E is widely distributed in food. The richest sources are vegetable oils especially wheat-germ oil (p.2415), sunflower oil, and cottonseed oil; cereals and nuts are also good sources. Significant losses of vitamin E from food may occur during cooking and storage.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI—see p.1925) nor an estimated average requirement (EAR) has been set for vitamin E although daily intakes of 4 mg and 3 mg α-tocopherol equivalents (see under Units, above) were considered adequate for men and women, respectively.[1] The Expert Group on Vitamins and Minerals[2] have established a safe upper level (SUL) for vitamin E of 800 units or 540 mg of *d*-alpha tocopherol daily.

In the USA the recommended dietary allowance for adults is 15 mg daily of alpha tocopherol, and the tolerable upper intake level is 1000 mg daily.[3]

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. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 09/01/06)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids.* Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)

Uses and Administration

Vitamin E, a fat-soluble vitamin, prevents the oxidation of polyunsaturated fatty acids. It reacts with free radicals, which are the cause of oxidative damage to cell membranes, without the formation of another free radical in the process.

Vitamin E deficiency is rare but develops when the dietary intake is inadequate. In children with cystic fibrosis or biliary atresia, malabsorption of fat may lead to a vitamin E deficiency; deficiency may also occur in children with abnormalities of lipid transport, as in abetalipoproteinaemia. Low vitamin E concentrations are also found in premature, very low birth-weight infants. In previously healthy adults malabsorption and low intake of vitamin E must continue for a number of years before signs of deficiency appear. The major signs of vitamin E deficiency are the development of myopathic and neurological disorders.

Vitamin E is used in the treatment and prevention of vitamin E deficiency. It is usually given orally, generally the preferred route, but has also been given by intramuscular or intravenous routes. It may be given as *d*- or *dl*-alpha tocopherol or as the respective acetates or acid succinates.

Recommended doses vary, in part because of differences in the activity of different preparations; however, a daily dose of several times the recommended dietary allowance (RDA), or around 40 to 50 mg of *d*-alpha tocopherol, has been suggested for deficiency syndromes; somewhat higher daily doses have been given

in cystic fibrosis (100 to 200 mg of *dl*-alpha tocoferil acetate, or about 67 to 135 mg of *d*-alpha tocopherol) and much higher daily doses in abetalipoproteinaemia (50 to 100 mg/kg of *dl*-alpha tocoferil acetate, or about 33 to 67 mg/kg *d*-alpha tocopherol).

Vitamin E has also been tried in retinopathy of prematurity and intraventricular haemorrhage in neonates (see Perinatal Disorders, below), and in many other disorders, for which the evidence of value is generally lacking (see Prophylaxis of Ischaemic Heart Disease, p.1926, and Prophylaxis of Malignant Neoplasms, p.1927).

Other substances with vitamin-E activity that have been used include *dl*-alpha tocoferil palmitate and tocofersolan (tocophersolan), a water-soluble substance which is *d*-alpha tocoferil acid succinate combined with a macrogol. Wheat-germ oil (p.2415) is also widely used as a source of vitamin E.

Vitamin E is often used as an antoxidant in pharmaceutical manufacturing.

◊ General reviews.

1. Meydani M. Vitamin E. *Lancet* 1995; **345:** 170–5.
2. Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. *J Physiol Biochem* 2001; **57:** 43–56.
3. Brigelius-Flohé R, *et al.* The European perspective on vitamin E: current knowledge and future research. *Am J Clin Nutr* 2002; **76:** 703–16.
4. Dutta A, Dutta SK. Vitamin E and its role in the prevention of atherosclerosis and carcinogenesis: a review. *J Am Coll Nutr* 2003; **22:** 258–68.
5. Sung L, *et al.* Vitamin E: the evidence for multiple roles in cancer. *Nutr Cancer* 2003; **46:** 1–14.

Age-related macular degeneration. Dietary supplementation with antoxidants including vitamin E has been promoted for age-related macular degeneration. For further details, see under Betacarotene, p.1931.

Chemotherapy-induced toxicity. A small pilot study[1] found that oral vitamin E 600 mg daily given during chemotherapy and for 3 months afterwards reduced chemotherapy-induced neuropathy in patients given regimens based on platinum (carboplatin or cisplatin), or paclitaxel, or both. The authors considered that similarities exist between neuropathy induced by cisplatin (and possibly paclitaxel) and that seen in vitamin E deficiency states, (see below). Oral vitamin E 300 mg daily alleviated palmar-plantar erythrodysesthesia in 5 patients given capecitabine and docetaxel.[2] In 4 of these patients, chemotherapy was continued without interruption or dose reduction. Improvement was generally noticed after 7 to 10 days of treatment.

1. Argyriou AA, *et al.* Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. *Neurology* 2005; **64:** 26–31.
2. Kara IO, *et al.* Palmar-plantar erythrodysesthesia due to docetaxel-capecitabine therapy is treated with vitamin E without dose reduction. *Breast* 2006; **15:** 414–24.

Deficiency states. Vitamin E deficiency may cause neurological damage characterised by sensory loss, ataxia and retinitis pigmentosa. In 2 patients with common variable immunodeficiency and an associated enteropathy, vitamin E deficiency developed. Treatment with intramuscular or oral vitamin E led to objective neurological improvement.[1]

1. Aslam A, *et al.* Vitamin E deficiency induced neurological disease in common variable immunodeficiency: two cases and a review of the literature of vitamin E deficiency. *Clin Immunol* 2004; **112:** 24–9.

Dementia. A hypothesis that free radicals may initiate and maintain mechanisms responsible for neurodegeneration in Alzheimer's disease (p.362) has prompted the investigation of various drugs for antoxidant therapy.[1] Preliminary studies[1,2] have suggested that alpha tocopherol might possibly slow progression. A prospective cohort study found that self-administration of combined vitamin C and vitamin E was associated with a lower risk of vascular dementia in elderly men,[3] although no significant protective effect was seen against Alzheimer's disease. However, other studies have suggested that high intake of vitamins C and E, whether from diet[4] or supplements,[5] may reduce the risk of Alzheimer's disease. Yet another study suggested that dietary vitamin E, but not vitamin C, intake reduced the risk of Alzheimer's disease;[6] a population-based study found vitamin E intake from food and supplements to be associated with reduced cognitive decline.[7] US guidelines suggested[8] that vitamin E 1000 units twice daily by mouth be considered in patients with Alzheimer's disease in an attempt to slow progression of the disease. However, a large randomised trial in patients with amnestic mild cognitive impairment found that vitamin E 2000 units daily provided no benefit over placebo in terms of probability of progression to Alzheimer's disease.[9] Reviewers[10,11] have recommended against the use of vitamin E for Alzheimer's disease.

1. Berman K, Brodaty H. Tocopherol (vitamin E) in Alzheimer's disease and other neurodegenerative disorders. *CNS Drugs* 2004; **18:** 807–25.
2. Sano M, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997; **336:** 1216–22.
3. Masaki KH, *et al.* Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology* 2000; **54:** 1265–72.
4. Engelhart MJ, *et al.* Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA* 2002; **287:** 3223–9.
5. Zandi PP, *et al.* Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County study. *Arch Neurol* 2004; **61:** 82–8.
6. Morris MC, *et al.* Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA* 2002; **287:** 3230–7.
7. Morris MC, *et al.* Vitamin E and cognitive decline in older persons. *Arch Neurol* 2002; **59:** 1125–32.
8. Doody RS, *et al.* Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; **56:** 1154–66. Also available at: http://www.neurology.org/cgi/reprint/56/9/1154.pdf (accessed 09/01/06)
9. Petersen RC, *et al.* Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; **352:** 2379–88.
10. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Ann Pharmacother* 2005; **39:** 2065–72.
11. Boothby LA, Doering PL. Vitamin C and vitamin E for Alzheimer's disease. *Ann Pharmacother* 2005; **39:** 2073–80.

Ischaemic heart disease. For a discussion of studies involving vitamin E in the prophylaxis of ischaemic heart disease, see p.1926.

Malignant neoplasms. For a discussion of studies involving vitamin E in the prophylaxis of malignant neoplasms, see p.1927.

Motor neurone disease. A prospective analysis found that regular use of vitamin E supplements was associated with a decreased risk of amyotrophic lateral sclerosis.[1] However, further studies were considered necessary and significant evidence to support the benefit of antoxidants in motor neurone disease (p.2380) is lacking.[2]

1. Ascherio A, *et al.* Vitamin E intake and risk of amyotrophic lateral sclerosis. *Ann Neurol* 2005; **57:** 104–10.
2. Orrell RW, *et al.* Antioxidant treatment for amyotrophic lateral sclerosis / motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 20/06/08).

Muscle spasm. Vitamin E is one of several drugs that have been tried in the management of nocturnal cramps (p.1887) but there is little convincing evidence to support its use.[1,2] It has, however, been found to have similar efficacy to quinine for haemodialysis-induced cramp (p.1671).[3] A small study found the combination of vitamins E and C to be more effective than either vitamin alone for reducing haemodialysis-induced cramps; prolonged use was not evaluated.[4]

1. Connolly PS, *et al.* Treatment of nocturnal leg cramps: a crossover trial of quinine vs vitamin E. *Arch Intern Med* 1992; **152:** 1877–80.
2. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; **59:** 43234–52.
3. Roca AO, *et al.* Dialysis leg cramps: efficacy of quinine versus vitamin E. *ASAIO J* 1992; **38:** M481–M485.
4. Khajehdehi P, *et al.* A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. *Nephrol Dial Transplant* 2001; **16:** 1448–51.

Muscular dystrophies. Vitamin E substances have been used in some countries in the management of muscular dystrophies, but controlled studies[1] have failed to demonstrate any benefit.

1. Örndahl G, *et al.* Functional deterioration and selenium-vitamin E treatment in myotonic dystrophy: a placebo-controlled study. *J Intern Med* 1994; **235:** 205–10.

Parkinsonism. Vitamin E has been tried (as *dl*-alpha tocopherol) in an attempt to slow neurodegeneration in patients with Parkinson's disease (p.791) but has proved ineffective.[1]

1. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.

Perinatal disorders. The primary biological action of vitamin E is known to be the protection of polyunsaturated fatty acids, and thus membranes, from oxidation. Two disorders that may particularly affect premature and very low birth-weight infants are *retinopathy of prematurity* (below) and *intraventricular haemorrhage* (p.1050) and as both may have some association with the occurrence of excess oxygen or oxidant stress, there has been interest in the possibility that vitamin E might have a role in their prevention.

Pre-eclampsia. Although preliminary evidence has suggested[1] that women supplemented with vitamin E (with other supplements) may be at decreased risk of developing clinical pre-eclampsia (see Hypertension in Pregnancy, p.1171), large studies[2,3] in women given combined vitamin C and vitamin E supplements failed to show any benefit.

1. Rumbold A, Crowther CA. Vitamin E supplementation in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 09/01/06).
2. Poston L, *et al.* Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 2006; **367:** 1145–54.
3. Rumbold AR, *et al.* ACTS Study Group. Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med* 2006; **354:** 1796–1806.

Respiratory-tract infections. A randomised study in elderly patients found that supplementation with vitamin E had no effect on the incidence of lower respiratory-tract infections in elderly nursing home residents, although there was some suggestion of benefit from supplementation on upper respiratory-tract infections, particularly the common cold.[1] In contrast, another study found that, among elderly non-institutionalised people with an acute respiratory-tract infection, vitamin E supplementation increased illness duration, number of symptoms, frequency of fever, and restricted activity.[2]

1. Meydani SN, *et al.* Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. *JAMA* 2004; **292:** 828–36. Correction. *ibid.*; 1305.
2. Graat JM, *et al.* Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA* 2002; **288:** 715–21.

Retinitis pigmentosa. Vitamin E has been tried in retinitis pigmentosa (p.1974) with conflicting results.

Retinopathy of prematurity. Retinopathy of prematurity (retrolental fibroplasia) is a disease associated with immature vascularisation of the retina. Formation of retinal lesions may interfere with normal development, resulting in neovascularisation and fibrovascular proliferation. Some cases regress spontaneously but advanced cases can lead to tractional retinal detachment and loss of vision. The pathogenesis of retinopathy of prematurity is not clearly understood, but is likely to be multifactorial;[1,2] greater immaturity, lower birth-weight, and male gender are associated with more severe disease.[3]

After the acknowledgement of a link between retinopathy of prematurity and oxygen therapy, the use of oxygen was reduced and the incidence of this disorder declined. A subsequent rise in incidence probably reflected the increased survival rate of extremely premature infants due to improved neonatal care, and certainly, variations in incidence between countries, or indeed areas, may reflect varying levels of available postnatal care.[2] Despite extensive research (see p.1690), a safe concentration of arterial oxygen has not been defined and antoxidants such as vitamin E have been used prophylactically for several decades. However, this use is controversial. Studies assessing the efficacy of vitamin E prophylaxis have not produced clear results.[4] Some considered that vitamin E prophylaxis had a beneficial effect and recommended[5] routine prophylaxis as soon as possible after birth for infants less than 1.5 kg. However, others feel that there is no data to support prophylaxis with vitamin E[4,6,7] and that antoxidants cannot be recommended for routine use.[1] The various studies have been re-evaluated by meta-analysis, the results of which suggest that vitamin E may reduce the incidence of stage 3+ retinopathy of prematurity,[8] a conclusion supported by a systematic review[9] which noted, however, that supplementation increased the risk of sepsis and could therefore not be recommended. The authors of the meta-analysis recommended that a well-controlled study should be conducted.[8] A systematic review of vitamin A supplementation in very low birth-weight infants concluded that vitamin A may reduce the incidence of retinopathy of prematurity, and that further investigation was warranted.[10]

Other agents tried for prophylaxis include penicillamine and antenatal dexamethasone, with some suggestion of benefit.[11,12] Reduction in ambient-light exposure did not alter the incidence of retinopathy of prematurity.[13,14] Inositol supplementation has also been tried, with conflicting results.[4]

1. Holmström G. Retinopathy of prematurity. *BMJ* 1993; **307:** 694–5.
2. Wheatley CM, *et al.* Retinopathy of prematurity: recent advances in our understanding. *Arch Dis Child Fetal Neonatal Ed* 2002; **87:** F78–F82.
3. Darlow BA, *et al.* Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. *Pediatrics* 2005; **115:** 990–6.
4. Reynolds JD. The management of retinopathy of prematurity. *Paediatr Drugs* 2001; **3:** 263–72.
5. Johnson L, *et al.* Effect of sustained pharmacologic vitamin E levels on incidence and severity of retinopathy of prematurity: a controlled clinical trial. *J Pediatr* 1989; **114:** 827–38.
6. Law MR, *et al.* Is routine vitamin E administration justified in very low-birthweight infants? *Dev Med Child Neurol* 1990; **32:** 442–50.
7. Ehrenkranz RA. Vitamin E and retinopathy of prematurity: still controversial. *J Pediatr* 1989; **114:** 801–3.
8. Raju TNK, *et al.* Vitamin E prophylaxis to reduce retinopathy of prematurity: a reappraisal of published trials. *J Pediatr* 1997; **131:** 844–50.
9. Brion LP, *et al.* Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 20/06/08).
10. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 14/03/08).
11. Higgins RD, *et al.* Antenatal dexamethasone and decreased severity of retinopathy of prematurity. *Arch Ophthalmol* 1998; **116:** 601–5.

12. Phelps DL, *et al*. D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).
13. Reynolds JD, *et al*. Lack of efficacy of light reduction in preventing retinopathy of prematurity. *N Engl J Med* 1998; **338:** 1572–6.
14. Phelps DL, Watts JL. Early light reduction for preventing retinopathy of prematurity in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).

Tardive dyskinesia. Reviews[1,2] on the use of vitamin E in the management of antipsychotic-induced tardive dyskinesia (see under Extrapyramidal Disorders, p.971) concluded that evidence of benefit has generally come from small studies with methodological problems. One review[1] concluded that whereas vitamin E may protect against deterioration of tardive dyskinesia there was no evidence that it produced symptomatic improvement. It was suggested[2] that vitamin E therapy may be most beneficial in those patients with tardive dyskinesia of less than 5-years duration. Some recommend vitamin E as a treatment option in patients with newly diagnosed disease.[3] Further large-scale studies are required to establish its place in treatment.

1. Soares KVS, McGrath JJ. Vitamin E for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 09/01/06).
2. Boomershine KH, *et al*. Vitamin E in the treatment of tardive dyskinesia. *Ann Pharmacother* 1999; **33:** 1195–1202.
3. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Ann Pharmacother* 2005; **39:** 2065–72.

Preparations

BP 2008: Alpha Tocopheryl Succinate Tablets;
USNF 26: Tocopherols Excipient;
USP 31: Vitamin E Capsules; Vitamin E Preparation.

Proprietary Preparations (details are given in Part 3)
Arg.: Antioxidante Natural; E-devit Protectora; Ephynal; Etec; Evion; Risordan†; Senexon E†; Tonovital E; ***Austral.:*** Bioglan Micelle E; Bioglan Natural E; Bioglan Water Soluble E; Chew-E; Dal-E; Macro E†; Mega E†; Vita E†; ***Austria:*** Avigilen; Ephynal; Etocomed; Evitol; Tocovenos; ***Belg.:*** Docviteee; Ephynal; Optovit E; ***Braz.:*** E Plus; E Radicaps; E-Mil†; E-Tabs; Eferol†; Emama; Ephynal; Fonto-Vit E; Fort E; Teutovit-E; Vieta; Vita-E; Vitizin E; Zirvit E; ***Canad.:*** Aquasol E; Kyolic Formula 106; Novo E; Nutrol E; One A Day Cholesterol Health†; Organex†; ***Chile:*** Crevet-E; Egogyn; Etec; ***Cz.:*** Biogelat Vitamin E†; Erevit; Evit†; Sant-E-Gal†; ***Fin.:*** Bio-E-Vitamin; Equiday; Esol†; Ido-E; Tokovitan; Vita-E†; ***Fr.:*** Dermorelle; Ephynal†; Toco; Tocolion; Tocopa; ***Ger.:*** Antioxidans E; Biopto-E; Biosan E; Detulin; E-Mulsin†; E-Tonil; E-Vicotrat; Elex E; Embial†; Ephynal†; Eplonat; Eusovit; Evion; Flexal Vitamin E; Malton E; Mowivit; Optovit; Puncto E; Sanavitan S; Spondyvit; Tocorell; Tocovital; Togasan; Uno-Vit; Vibolex E; Vita-E; Vitagutt Vitamin E†; Vitazell E; ***Gr.:*** E-Vicotrat; Ephynal†; Eviol; ***Hong Kong:*** Clinic†; Keri Vit E; Myra 300-E; Natopherol; Topher-E; ***India:*** Ecap; EEE; Evion; Evitam; Greenpearl†; ***Indon.:*** Bio-E; Dalfarol; Edoti; Evion; Evipon; Lanturol; Natopherol; Natur-E; Naturol; Prima-E; Proxidan; Santa-E; Tocopherine; Vinpo-E; Vitaferol; ***Irl.:*** Ephynal†; ***Israel:*** Ephynal†; Evitex; Evitol; ***Ital.:*** E-Vitum; Ephynal; Evasen Crema; Evion; Natovit; Rigentex; Sursum; ***Malaysia:*** Citrex Vitamin E; E Vita†; Fairy ADE; Juvela†; Natopherol; Toco-E; ***Mex.:*** Bacferol†; E-Fertoc; Egrin; EPH; Eugerminol†; Ixopolet; Revitare E; Vit-E-Far; Vitalle†; ***Norw.:*** Bio-E-Vitamin; Ido-E; Nycoplus E; ***NZ:*** Micelle E; ***Philipp.:*** Enat; Enervon-E; Evion; Myra; Zyme E; ***Pol.:*** Dermovit E; Tokovit E; Vitole E; ***Port.:*** Ephynal; Ve; ***Rus.:*** Evitol (Эвитол); ***S.Afr.:*** Ephynal; Vitaforce E; ***Singapore:*** Myra 300-E; Natopherol; Naturee; ***Spain:*** Auxina E; Ephynal; ***Swed.:*** E-vidon; E-vimin; Ido-E; ***Switz.:*** ecobiosan; Ephynal; Evit; Lipo E†; Optovit; ***Thai.:*** Bio-E; E-Drops; ***Turk.:*** Eforol; Ephynal; Evicap; Evigen; Evon; Grandpherol; Natural E; Natural Wealth; ***UK:*** Ephynal; Prairie Gold; Vita-E; ***USA:*** Aqua-E; Aquasol E; Aquavit-E; E-Gems; Nutr-E-Sol; Vita-Plus E; Vitec; ***Venez.:*** Best; Ecogyn†; Egogyn; Ephynal†; Epol; Missecap; Nat-E; Vit-E-Nat; Vit-E-Var; Vitae; Viteral.

Multi-ingredient: ***Arg.:*** A-Vitel E; Abanta; Acilac; Atomoderma A-E; Brunavera; Cardiax; Cellskinlab C + E; Centella Asiatica Diates; Centella Asiatica Vital; Centellase de Centella Queen; Crema De Ordene; Culuflex H; Dermanova; E-devit; Epitheliale A-Derma; Estri-Atlas; Eurocolor Bronceador; Factor Vit AE; Lipofundin MCT/LCT-E; Liposomas; Nectar G; Oxidermos; Redudiet; SCV 300; Sigmafem; Snella; Snella Vag; Sojasterol†; Solenil Post Solar; Vansame; VNS 45; ***Austral.:*** Althaea Complex; Antioxidant Forte Tablets; Antioxidant Tablets; Arthriforte; Beta A-C; Bioglan Bioage Peripheral; Bioglan Micelle A plus E; Bioglan Primrose-E; Curash Baby Wipes; Curash Babycare; ER Cream†; Eye Health Herbal Plus Formula 4; Ginkgo Complex†; Hair and Skin Formula†; Lifechange Circulation Aid†; Lifesystem Herbal Plus Formula 5 Eye Relief†; Lifesystem Herbal Plus Formula 8 Echinacea†; Macro Natural Vitamin E Cream; ML 20†; Sambucus Complex†; Serenoa Complex†; ***Austria:*** A-E-Mulsin; Arcavit A/E; Coldistop; Droxaryl; Gerogelat; Mamellin; Pasuma-Dragees; Regenerin†; Rovigon; Ulcurilen; Vasovitol; ***Belg.:*** Rovigon; ***Braz.:*** Adeforte; Licovit; ***Canad.:*** Bionagre plus E; Lubriderm Advanced Moisture†; PML Crono†; ***Chile:*** Dermaglos; Dermaglos Plus†; Rovigon; ***Cz.:*** A-E-Mulsin†; Coldastop; Dr Theiss Beinwell Salbe†; Fluocaril Bi-Fluore Vitamin E†; Lipovitan†; Vitazulen†; ***Fin.:*** Aesol; Cellavie†; ***Fr.:*** Alpha 5 DS†; Bakol; BiaZinc†; Bio-Selenium; Cicatryl; Cirkan a la Prednacinolone; Difrarel E; Ophtadil†; Phytolongbronze; Phytosolaire; Reti-Nat; Rovigon†; Seborheane; Tonimer; Topialyse; Topialyse Fluide; Topialyse Plus; ***Ger.:*** A + E Thilo†; A-E-Mulsin†; anabol-loges; Coldastop; Dynef†; Hewekzem novo N; Lipidavit; Lipovitan†; Magnesium Tonil mit Vitamin E; Magnesium-Plus-Hevert; Mapurit; NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; NeyPulpin N (Revitorgan-Dilutionen N Nr 10)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; Protecor; Remederm; Rovigon G†; RubieMag + E†; Salus Herz-Schutz-Kapseln†; Saluscor Herz-Schutz; Tears Again; Ulcurilen N†; Unguentacid; Ureata S†; Vaso-E-Bion; ***Gr.:*** Avegon; Eviol-A; ***Hong Kong:*** Aderma Epitheliale†; Apaisac; Basikol; Difrarel E; Doctor's Choice Omega 3; DS Emulsion; E-Prime†; Eye Q; Pilelife; Pregnacare; Sanjukei Panax Ginseng; Welsan Lipocream; ***Hung.:*** Alksebor; Coldastop; Difrarel E; Magnevital; ***India:*** Cadvion; Elovera; Elovera-SPF; Rovigon†; Sclerobion; Seaking Plus†; Sofderm; Vitexid; ***Indon.:*** Fundamin-E; Garlic-Plus; Hepamax; Jointfit; Juvelon-C; Lanakeloid-E; Lapibion; Legreskin; Lesifit; Lycoq; Nervitone E; Remasal; RG-Q; Tocobion; Trimate-E; Velostin; Voldilex; ***Ital.:*** Angstrom Viso; Apogeo; Babysteril; Capill; Colesterase; Coqun; Derman-Oil; Dermana Crema; Dermana Pasta; Ecamannan; Efagel; Emortrofine; Ener-E†; Eurogel; Forticrin; Granoleina†; Ictom 3†; Midium; Migel; Mirtilene; Pasta Dicofarm; Provitamin A-E; Retinovit; Rovigon; Royal E; Rutisan CE†; Skarflex; Tannidin Plus; Tocalfa; Ultravisin; Vasopt; Vit Eparin; ***Malaysia:*** Balance Elastin E†; Boots Antenatal Massage Cream†; Elovera; Natopherol Dermal-Day†; Prim E; Salonpas; Tocovid; ***Mex.:*** Aveendix; Cardioprotect; Cetopic; Emolin Neo; Hipoglos Cremoso; Nutrem; Panaline†; Periodentyl; ***Neth.:*** Dagravit A-E Forte†; ***NZ:*** Chap Stick; ***Philipp.:*** Elovera; Hinuron-E; Neuroforte-E; Nuron-E; Pynocare 40 Actisome; Remederm; Rovigon; ***Pol.:*** Capivit A + E; Dehalid†; Lecytyna E; MBE; Tokovit A + E; ***Port.:*** Alkagin; Antiestrias; Creme Laser Hidrante; Esclerobion; Nutraisdin; Rilastil Dermo Solar; Rovigon; Synchrorose; Synchrovit; Zolium†; ***Singapore:*** Desitin Creamy†; E-Prime; Erase; ***Spain:*** Auxina A + E; Vitaber A E; Wobenzimal†; ***Switz.:*** Alphastria; Coldistop; Leniderm†; Oravil; Rovigon; Visaline; ***Thai.:*** Men Hormone; Siduol; ***UK:*** Octacosanol; Se-Power; ***USA:*** Aloe Grande; Diaper Guard; Lactinol-E; Lazercreme; Lobana Derm-Aide; Lobana Peri-Garde; Phicon; Tucks; Wound Cleanser; Ze Caps†; ***Venez.:*** Ademina; Kalsis.

Vitamin K Substances

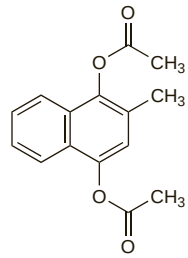
Vitamina K.

The term vitamin K is used for a range of naphthoquinone compounds that includes: acetomenaphthone, menadiol, menadione, menatetrenone, and phytomenadione.

Acetomenaphthone *(BAN)*

Acetomenadione; Acetomenaftona; Acetomenaph.; Menadiol Diacetate; Vitamin K_4 Diacetate. 2-Methyl-1,4-naphthylene diacetate.

$C_{15}H_{14}O_4$ = 258.3.
CAS — 573-20-6.

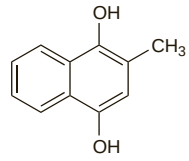


Pharmacopoeias. In *Chin.*

Menadiol Sodium Phosphate *(BANM)*

Menadiol, fosfato sódico de; Menadiol Sodium Diphosphate; Menadiolum Solubile; Vitamin K_4 Sodium Phosphate. 2-Methylnaphthalene-1,4-diyl bis(disodium phosphate) hexahydrate.

$C_{11}H_8Na_4O_8P_2,6H_2O$ = 530.2.
CAS — 481-85-6 (menadiol); 131-13-5 (anhydrous menadiol sodium phosphate); 6700-42-1 (menadiol sodium phosphate hexahydrate); 84-98-0 (menadiol diphosphate).



(menadiol)

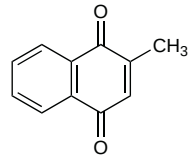
NOTE. Menadiol Potassium Sulfate (Potassium Menaphthosulfate) is *BAN* and Menadiol Sodium Sulfate is *rINN*.

Pharmacopoeias. In *Br.* and *US.*
BP 2008 (Menadiol Sodium Phosphate). A white to pink, hygroscopic, crystalline powder with a characteristic odour. Very soluble in water; practically insoluble in alcohol.
USP 31 (Menadiol Sodium Diphosphate). A white to pink, hygroscopic, powder having a characteristic odour. Very soluble in water; insoluble in alcohol. Its solutions in water are neutral or slightly alkaline to litmus having a pH of about 8. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Menadione *(BAN)*

Menadion; Menadiona; Menadionas; Ménadione; Menadioni; Menadionum; Menaph.; Menaphthene; Menaphthone; Methylnaphthochinonum; Vitamin K_3. 2-Methyl-1,4-naphthoquinone.

$C_{11}H_8O_2$ = 172.2.
CAS — 58-27-5.
ATC — B02BA02.
ATC Vet — QB02BA02.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Menadione). A pale yellow crystalline powder. It is unstable in light. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in toluene. Protect from light.
USP 31 (Menadione). A bright yellow, practically odourless, crystalline powder. It is affected by sunlight. Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 50 of vegetable oils, and 1 in 10 of benzene; sparingly soluble in chloroform. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Handling. Menadione powder is irritating to the respiratory tract and to the skin. The alcoholic solution has vesicant properties.

Menadione Sodium Bisulfite *(rINN)*

Bisulfito sódico de menadiona; Kavitanum; Menadiol Sodyum Bisülfit; Ménadione, Bisulfite Sodique de; Menadione Sodium Bisulphite *(BANM)*; Menadioni Natrii Bisulfis; Menadioninatriumbisulfiitti; Menadionnatriumbisulfit; Menadionu wodorosiarczyn sodowy; Menaph. Sod. Bisulphite; Menaphthone Sodium Bisulphite; Methylnaphthochinonumnatrium Bisulfurosum; Vikasolum; Vitamin K_3 Sodium Bisulphite. Sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxonaphthalene-2-sulphonate trihydrate.

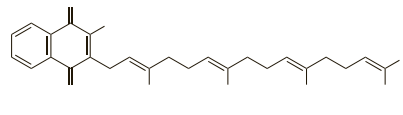
Менадиона Натрия Бисульфит
$C_{11}H_8O_2NaHSO_3,3H_2O$ = 330.3.
CAS — 130-37-0 (anhydrous menadione sodium bisulfite); 6147-37-1 (menadione sodium bisulfite trihydrate).

Pharmacopoeias. In *Chin.* and *Pol.*

Menatetrenone *(rINN)*

E-3100; Ea-0167; Menaquinone-4; Menaquinone 4; Menaquinone K4; Menatetren; Menatetrenona; Ménatétrénone; Menatetrenonum; MK-4; Vitamin $K_{2(20)}$; Vitamin MK 4. 2-Methyl-3-(3,7,11,15-tetramethyl-2,6,10,14-hexadeca-tetraenyl)-1,4-naphthoquinone.

Менатетренон
$C_{31}H_{40}O_2$ = 444.6.
CAS — 863-61-6.

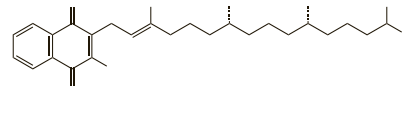


Pharmacopoeias. In *Jpn.*

Phytomenadione *(BAN, rINN)*

Fitomenadion; Fitomenadiona; Fitomenadionas; Fytomenadion; Fytomenadioni; Methylphytylnaphthochinonum; Phylloquinone; Phytomenad.; Phytoménadione; Phytomenadionum; Phytonadione; Vitamin K_1. 2-Methyl-3-[3,7,11,15-tetramethylhexadec-2-enyl] naphthalene-1,4-dione.

Фитоменадион
$C_{31}H_{46}O_2$ = 450.7.
CAS — 84-80-0.
ATC — B02BA01.
ATC Vet — QB02BA01.



Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*
Ph. Eur. 6.2 (Phytomenadione). A mixture of the *trans* (*E*) and *cis* (*Z*) isomers. It contains not less than 75% of *trans*-phytomenadione, and also allows not more than 4% of *trans*-epoxyphytomenadione.
A clear, intense yellow, viscous, oily liquid, which decomposes on exposure to actinic light. Practically insoluble in water; sparingly soluble in alcohol; miscible with fatty oils. Protect from light.
USP 31 (Phytonadione). A mixture of the *E* and *Z* isomers. It contains not more than 21% of the *Z* isomer. A clear, yellow to