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

Ph. Eur. 6.2 (Hydroxocobalamin Sulphate). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble in water. Some decomposition may occur on drying. Store at a temperature between 2° and 8° in airtight containers. Protect from light.

Mecobalamin *(BAN, USAN, pINN)*

Mecobalamina; Mécobalamine; Mecobalaminum; Methylcobalamin. *Co*α-[α-(5,6-Dimethylbenzimidazolyl)]-*Co*β-methylcobamide.

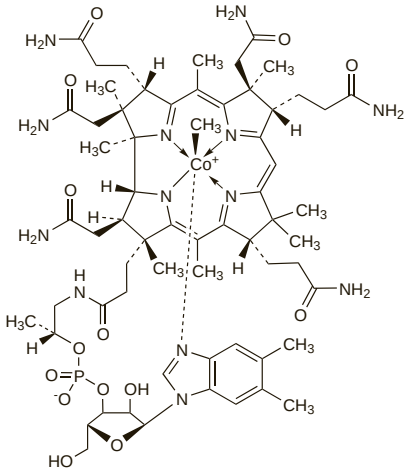
Мекобаламин

$C_{63}H_{91}CoN_{13}O_{14}P$ = 1344.4.

CAS — 13422-55-4.

ATC — B03BA05.

ATC Vet — QB03BA05.



Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

Allergic hypersensitivity reactions have occurred rarely after parenteral doses of the vitamin B_{12} compounds cyanocobalamin and hydroxocobalamin. Antibodies to hydroxocobalamin-transcobalamin II complex have developed during hydroxocobalamin therapy.

Arrhythmias secondary to hypokalaemia have occurred at the beginning of parenteral treatment with hydroxocobalamin.

Intranasal cyanocobalamin may cause rhinitis, nausea, and headache.

Cyanocobalamin or hydroxocobalamin should, if possible, not be given to patients with suspected vitamin B_{12} deficiency without first confirming the diagnosis. Regular monitoring of the blood is advisable. Use of doses greater than 10 micrograms daily may produce a haematological response in patients with folate deficiency; indiscriminate use may mask the precise diagnosis. Conversely, folate may mask vitamin B_{12} deficiency (see p.1940).

Cyanocobalamin should not be used for Leber's disease or tobacco amblyopia since these optic neuropathies may degenerate further.

Breast feeding. Vitamin B_{12} is distributed into breast milk.[1] The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.[2]

1. Samson RR, McClelland DBL. Vitamin B in human colostrum and milk. *Acta Paediatr Scand* 1980; **69:** 93–9.
2. 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)

Hypersensitivity. Analysis, by the Boston Collaborative Drug Surveillance Program, of data on 15 438 patients hospitalised between 1975 and 1982 detected 3 allergic skin reactions attributed to cyanocobalamin among 168 recipients of the drug.[1] For the purposes of the study, reactions were defined as being generalised morbilliform exanthems, urticaria, or generalised pruritus only.

In a patient with a generalised pruritic reaction to hydroxocobalamin (with subsequent urticaria, bronchospasm, and oropharyngeal angioedema), cyanocobalamin was relatively well-tolerated, with only one episode of delayed urticaria.[2]

1. Bigby M, *et al*. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256:** 3358–63.
2. Heyworth-Smith D, Hogan PG. Allergy to hydroxycobalamin, with tolerance of cyanocobalamin. *Med J Aust* 2002; **177:** 162–3.

Local reactions. After 3 years of monthly intramuscular vitamin B_{12} injections, a patient presented with a sclerotic plaque at the injection site, which was successfully treated by excision and local fat transfer. It was unclear as to whether the patient had reacted to the vehicle, the preservative, or to the cyanocobalamin.[1] Fascial haematoma after vitamin B_{12} injection leading to local compression (posterior arm compartment syndrome) has also been reported.[2]

1. Ho J, *et al*. Vitamin B12-associated localized scleroderma and its treatment. *Dermatol Surg* 2004; **30:** 1252–5.
2. Knapke D, Truumees E. Posterior arm and deltoid compartment syndrome after vitamin B12 injection. *Orthopedics* 2004; **27:** 520–1.

Interactions

Absorption of vitamin B_{12} from the gastrointestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H_2-antagonists, omeprazole, and colchicine. Serum concentrations may be decreased by use of oral contraceptives. Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations. Parenteral chloramphenicol may attenuate the effect of vitamin B_{12} in anaemia.

Pharmacokinetics

Vitamin B_{12} substances bind to intrinsic factor, a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically. After intranasal dosage, peak plasma concentrations of cyanocobalamin have been reached in 1 to 2 hours. The bioavailability of the intranasal preparation is about 7 to 11% of that by intramuscular injection.

Vitamin B_{12} is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Vitamin B_{12} is stored in the liver, excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Vitamin B_{12} diffuses across the placenta and also appears in breast milk.

Retention in the body. After injection of cyanocobalamin a large proportion is excreted in the urine within 24 hours; the body retains only 55% of a 100-microgram dose and 15% of a 1000-microgram dose. Body stores of vitamin B_{12} amount to 2000 to 3000 micrograms which is believed to be enough for 3 to 4 years. If 1000 micrograms is injected monthly, the 150 micrograms retained lasts for about 1 month. Hydroxocobalamin is better retained than cyanocobalamin; 90% of a 100-microgram dose and 30% of a 1000-microgram dose are retained and that range is believed to be enough for 2 to 10 months.[1]

1. Anonymous. Time to drop cyanocobalamin? *Drug Ther Bull* 1984; **22:** 43.

Human Requirements

For adults, the daily requirement of vitamin B_{12} is probably about 1 to 2 micrograms and this amount is present in most normal diets. Vitamin B_{12} occurs only in animal products; it does not occur in vegetables, therefore strict vegetarian (vegan) diets that exclude dairy products may provide an inadequate amount although it has been said that many years of vegetarianism are necessary before a deficiency is produced, if at all. Meats, especially liver and kidney, milk, eggs, and other dairy products, and fish are good sources of vitamin B_{12}.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p.1925) have been published for vitamin B_{12} and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, adults and pregnant and lactating women. In the UK the reference nutrient intake (RNI) is 1.5 micrograms daily for adult males and females and the estimated average requirement (EAR) is 1.25 micrograms daily. In the USA the RDA for adults is 2.4 micrograms daily.

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 thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Uses and Administration

Vitamin B_{12}, a water-soluble vitamin, occurs in the body mainly as methylcobalamin (mecobalamin) and as adenosylcobalamin (cobamamide) and hydroxocobalamin. Mecobalamin and cobamamide act as coenzymes in nucleic acid synthesis. Mecobalamin is also closely involved with folic acid in several important metabolic pathways.

Vitamin B_{12} deficiency can occur in strict vegetarians with an inadequate dietary intake, although it may take many years before a deficiency is produced. Deficiency is more likely in patients with malabsorption syndromes or metabolic disorders, nitrous oxide-induced megaloblastosis, or after gastrectomy or extensive ileal resection. Deficiency leads to the development of megaloblastic anaemias and demyelination and other neurological damage. A specific anaemia known as pernicious anaemia develops in patients with an absence of the intrinsic factor necessary for good absorption of the vitamin from dietary sources.

Vitamin B_{12} preparations are used in the treatment and prevention of vitamin B_{12} deficiency. It is essential to identify the exact cause of deficiency, preferably before starting therapy. Hydroxocobalamin is generally preferred to cyanocobalamin; it binds more firmly to plasma proteins and is retained in the body longer (see under Pharmacokinetics, above). Cyanocobalamin and hydroxocobalamin are generally given by the intramuscular route, although cyanocobalamin may be given orally or subcutaneously, or intranasally (see also under Administration, below). Oral cyanocobalamin may be used in treating or preventing vitamin B_{12} deficiency of dietary origin.

In the UK, recommended doses for **pernicious anaemia** and other macrocytic anaemias *without neurological involvement* are hydroxocobalamin (or cyanocobalamin) 250 to 1000 micrograms intramuscularly on alternate days for 1 to 2 weeks, then 250 micrograms weekly until the blood count returns to normal. Maintenance doses of 1000 micrograms of hydroxocobalamin are given every 2 to 3 months (or monthly for cyanocobalamin). If there is *neurological involvement*, hydroxocobalamin or cyanocobalamin may be given in doses of 1000 micrograms on alternate days and continued for as long as improvement occurs. For the *prophylaxis* of anaemia associated with vitamin B_{12} deficiency resulting from gastrectomy or malabsorption syndromes hydroxocobalamin may be given in doses of 1000 micrograms intramuscularly every 2 or 3 months or cyanocobalamin in doses of 250 to 1000 micrograms intramuscularly each month. For vitamin B_{12} deficiency of *dietary* origin, oral cyanocobalamin 50 to 150 micrograms may be taken daily between meals.

Lower doses of both cyanocobalamin and hydroxocobalamin are recommended in the USA. For the *treatment* of deficiency, the usual intramuscular or subcutaneous dose of cyanocobalamin is 100 micrograms

daily for 7 days, then on alternate days for 7 further doses, then every 3 to 4 days for 2 to 3 weeks. For hydroxocobalamin the usual intramuscular dose is 30 micrograms daily for 5 to 10 days. For *maintenance*, both cyanocobalamin and hydroxocobalamin are given at a dose of 100 to 200 micrograms monthly, based on haematological monitoring. Intranasal preparations of cyanocobalamin are also available for maintenance therapy, the recommended dose being 500 micrograms once weekly. Oral doses of up to 1000 micrograms of cyanocobalamin have also been used. In patients with normal gastrointestinal absorption, doses of 1 to 25 micrograms daily are considered sufficient as a *dietary supplement.*

Treatment usually results in rapid haematological improvement and a striking clinical response. However, neurological symptoms respond more slowly and in some cases remission may not be complete.

Cobamamide and mecobalamin may also be used for vitamin B_{12} deficiency.

Hydroxocobalamin may also be given in the treatment of **tobacco amblyopia** and **Leber's optic atrophy**; initial doses are 1000 micrograms daily for 2 weeks intramuscularly followed by 1000 micrograms twice weekly for as long as improvement occurs. Thereafter, 1000 micrograms is given every 1 to 3 months.

Hydroxocobalamin is also used for the treatment of known or suspected **cyanide toxicity** (see below). Each 2.5 g vial of hydroxocobalamin is reconstituted with 100 mL of diluent, preferably sodium chloride 0.9%. The starting dose for adults is 5 g intravenously over 15 minutes. Depending on the severity of the toxicity and the clinical response, a second dose of 5 g may be infused over 15 minutes to 2 hours.

Cyanocobalamin and hydroxocobalamin are also used in the **Schilling test** to investigate vitamin B_{12} absorption and deficiency states. They are given in a non-radioactive form together with cyanocobalamin radioactively-labelled with cobalt-57 (p.2053) or cobalt-58 (p.2053) and the amount of radioactivity excreted in the urine can be used to assess absorption status. A differential Schilling test, in which the forms of cyanocobalamin are given under different conditions (such as with intrinsic factor, antibacterials, or pancreatic enzymes) can provide information concerning the cause of the malabsorption.

Administration. The small amounts of vitamin B_{12} present in the diet are absorbed from the gastrointestinal tract by an active process that involves binding with intrinsic factor. As intrinsic factor is absent in patients who have developed pernicious anaemia it has often been assumed that oral vitamin B_{12} preparations will therefore be ineffective. However, about 1% of an oral dose is absorbed by passive diffusion, and with large doses this amount may be sufficient for therapy. Thus attention has been given again to the use of oral cobalamins for the treatment of pernicious anaemia.[1-3] Oral cyanocobalamin 2000 micrograms daily was as effective as intramuscular therapy in patients with vitamin B_{12} deficiency in a comparative study.[4] Some now consider that oral doses of 1000 micrograms daily,[3,5] or every 2 weeks for children,[6] are a suitable alternative to injections given at monthly or so intervals; others still deem oral use to be unjustified on the grounds of negligible oral absorption.[7] A systematic review[8] of 2 studies found some evidence for a satisfactory haematological, biochemical, and clinical short-term response to oral replacement in some patients with conditions associated with malabsorption. Another review[9] concluded that, while there is substantial evidence to support the use of 1000 to 2000 micrograms daily of oral cobalamin as maintenance therapy, parenteral therapy is preferable for initial treatment of those with neurological symptoms. Cyanocobalamin is also effective when given intranasally,[10] with peak plasma concentrations greater than those achievable orally, and this may offer another alternative to injection. The intranasal absorption of hydroxocobalamin has been studied.[11,12] Cobalamin has also been given sublingually. Normalisation of serum cobalamin concentration has been reported in 18 patients given cyanocobalamin 2000 micrograms sublingually for 7 to 12 days;[13] 500 micrograms sublingually was found to be as effective as the same dose given orally in correcting cobalamin deficiency.[14]

1. Lederle FA. Oral cobalamin for pernicious anemia: medicine's best kept secret? *JAMA* 1991; **265:** 94–5.
2. Hathcock JN, Troendle GJ. Oral cobalamin for treatment of pernicious anemia? *JAMA* 1991; **265:** 96–7.
3. Elia M. Oral or parenteral therapy for B12 deficiency. *Lancet* 1998; **352:** 1721–2.
4. Kuzminski AM, *et al.* Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998; **92:** 1191–8.
5. Andrès E, *et al.* Usefulness of oral cyanocobalamin therapy in severe hematologic manifestations related to vitamin B deficiency. *Ann Pharmacother* 2004; **38:** 1086–7.
6. Çetin M, Altay C. Efficacy of oral vitamin B treatment in children. *J Pediatr* 2001; **139:** 754.
7. Van der Kuy P-HM, *et al.* Bioavailability of oral hydroxocobalamin. *Br J Clin Pharmacol* 2000; **49:** 395P–396P.
8. Vidal-Alaball J, *et al.* Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 05/09/06).
9. Lane LA, Rojas-Fernandez C. Treatment of Vitamin B -deficiency anemia: oral versus parenteral therapy. *Ann Pharmacother* 2002; **36:** 1268–72.
10. Romeo VD, *et al.* Intranasal cyanocobalamin. *JAMA* 1992; **268:** 1268–9.
11. van Asselt DZB, *et al.* Nasal absorption of hydroxocobalamin in healthy elderly adults. *Br J Clin Pharmacol* 1998; **45:** 83–6.
12. Slot WB, *et al.* Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. *Gastroenterology* 1997; **113:** 430–3.
13. Delpre G, *et al.* Sublingual therapy for cobalamin deficiency as an alternative to oral and parenteral cobalamin supplementation. *Lancet* 1999; **354:** 740–1.
14. Sharabi A, *et al.* Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. *Br J Clin Pharmacol* 2003; **56:** 635–8.

Amino acid metabolic disorders. References to the use of hydroxocobalamin in the treatment of inborn errors of vitamin B_{12} metabolism.[1-3] Some patients with homocystinuria (p.1922) or methylmalonic aciduria have responded to cobalamins—the *BNFC* suggests an initial intramuscular dose of 1 mg daily, for 5 to 7 days, in patients from one month of age; this is reduced, according to response, to 1 mg once or twice weekly. Some children respond to maintenance with 5 to 10 mg once or twice weekly by mouth.

1. Linnell JC, Bhatt HR. Inherited errors of cobalamin metabolism and their management. *Baillieres Clin Haematol* 1995; **8:** 567–601.
2. Andersson HC, Shapira E. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylmalonic acidemia and homocystinuria (cblC). *J Pediatr* 1998; **132:** 121–4.
3. Smith DL, Bodamer OA. Practical management of combined methylmalonicaciduria and homocystinuria. *J Child Neurol* 2002; **17:** 353–6.

Cardiovascular disease. For mention of the possible link between vitamin B_{12}, hyperhomocysteinaemia, and cardiovascular disease, see under Folic Acid p.1941.

Cyanide toxicity. Hydroxocobalamin combines with cyanide to form cyanocobalamin, and thus may be used as an antidote to cyanide toxicity (p.2045). Hydroxocobalamin is reported to be effective in controlling cyanide toxicity due to nitroprusside infusion,[1] and after exposure to inhaled combustion products in residential fires.[2]

It has been hypothesised that the amount of cyanocobalamin formed is limited by the number of cyanide ions present and the amount of hydroxocobalamin given. For a given dose of hydroxocobalamin a maximum concentration of cyanocobalamin would be reached, allowing measurement of cyanocobalamin as a surrogate emergency marker for cyanide levels, which are difficult and time-consuming to measure. For a 5-g dose of hydroxocobalamin given intravenously over 30 minutes, the authors of one study considered a cyanocobalamin concentration of about 300 micromoles/litre a sign that all the hydroxocobalamin had been used, and more should be given.[2] They cautioned, however, that, unless antidote regimen and blood sampling were similar to that in their study, this concentration should not be extrapolated to other patient populations.

In another patient given hydroxocobalamin 5 g intravenously over 2 hours,[3] plasma concentrations of cyanide rose 1 hour after treatment with hydroxocobalamin. The authors attributed this to hydroxocobalamin extracting cyanide from red blood cells to form cyanocobalamin in plasma, which was then measured as cyanide.

1. Zerbe NF, Wagner BKJ. Use of vitamin B12 in the treatment and prevention of nitroprusside-induced cyanide toxicity. *Crit Care Med* 1993; **21:** 465–7.
2. Houeto P, *et al.* Relation of blood cyanide to plasma cyanocobalamin concentration after a fixed dose of hydroxocobalamin in cyanide poisoning. *Lancet* 1995; **346:** 605–8.
3. Weng T-I, *et al.* Elevated plasma cyanide after hydroxocobalamin infusion for cyanide poisoning. *Am J Emerg Med* 2004; **22:** 492–3.

Deficiency states. The emergence of newer metabolic assays for homocysteine and methylmalonic acid has led to the identification of subtle vitamin B_{12} deficiency[1-3] without the overt manifestations of megaloblastic anaemia (see below) or neurological disease; this condition appears to be particularly common in the elderly.[1,4-6] At present, there is no clear clinical rationale for treating subtle deficiency.[1,7] A study in elderly patients suggested that food-cobalamin malabsorption, a disorder characterised by the inability to release vitamin B_{12} from food or its binding protein, might be to blame for this subtle deficiency; these patients had some neurological or haematological abnormalities, and treatment with oral or parenteral vitamin B_{12} was found to be effective.[6] There have also been suggestions that deficiency may be linked to some immunological impairment, identified as impaired antibody responses to pneumococcal vaccine.[8] Moreover, raised homocysteine concentrations have been identified as a risk factor for atherosclerosis and ischaemic heart disease, and there is increasing interest in the potential of B vitamins, including B_{12}, to reduce homocysteine concentrations and therefore atherosclerotic outcomes (see Cardiovascular Disease, under Uses of Folic Acid, p.1941). Evidence that hyperhomocysteinaemia may be a risk factor for dementia is limited.[5] A systematic review concluded that evidence for efficacy of vitamin B_{12} in improving cognitive function of people with dementia (and low serum vitamin B_{12} concentrations) was lacking.[9]

Dietary vitamin B_{12} deficiency in infants may lead to developmental abnormalities.[10,11]

The issue of fortification of food with folic acid to reduce the number of infants born with neural tube defects has created debate on the risks of masking vitamin B_{12} deficiency, and fortification with vitamin B_{12} has also been recommended, see under Folic Acid, p.1940.

1. Carmel R. Subtle cobalamin deficiency. *Ann Intern Med* 1996; **124:** 338–40.
2. Green R. Screening for vitamin B deficiency: caveat emptor. *Ann Intern Med* 1996; **124:** 509–11.
3. Carmel R, *et al.* Update on cobalamin, folate, and homocysteine. *Hematology (Am Soc Hematol Educ Program)* 2003; 62–81.
4. Andrès E, *et al.* Vitamin B (cobalamin) deficiency in elderly patients. *Can Med Assoc J* 2004; **171:** 251–9.
5. Clarke R. Prevention of vitamin B-12 deficiency in old age. *Am J Clin Nutr* 2001; **73:** 151–2.
6. Andrès E, *et al.* Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. *Am J Med* 2005; **118:** 1154–9.
7. Metz J. What's the use of oral vitamin B ? A neglected but valid treatment route may have new uses in the future. *Med J Aust* 1999; **170:** 407.
8. Fata FT, *et al.* Impaired antibody responses to pneumococcal polysaccharide in elderly patients with low serum vitamin B levels. *Ann Intern Med* 1996; **124:** 299–304.
9. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 09/01/06).
10. Emery ES, *et al.* Vitamin B12 deficiency: a cause of abnormal movements in infants. *Pediatrics* 1997; **99:** 255–6.
11. von Schenck U, *et al.* Persistence of neurological damage induced by dietary vitamin B-12 deficiency in infancy. *Arch Dis Child* 1997; **77:** 137–9.

Eczema. A small study found that topical application of a preparation containing vitamin B_{12} was more effective than placebo in patients with atopic eczema.[1]

1. Stücker M, *et al.* Topical vitamin B —a new therapeutic approach in atopic dermatitis—evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. *Br J Dermatol* 2004; **150:** 977–83.

Megaloblastic anaemia. The megaloblastic anaemias are characterised by macrocytosis (an increased mean cell volume) and the production of distinctive morphological changes and abnormal maturation in developing haematopoietic cells in the bone marrow: white cell and platelet lines are affected as well as erythroid precursors, and in severe cases anaemia may be associated with leucopenia and thrombocytopenia. Megaloblastic anaemia is a consequence of impaired DNA biosynthesis in the bone marrow, usually due to a deficiency of vitamin B_{12} (cobalamins) or folate, both of which are essential for this process. Although the haematological symptoms of B_{12} deficiency and folate deficiency are similar it is important to distinguish between them since the use of folate alone in B_{12}-deficient megaloblastic anaemia can improve haematological symptoms without preventing aggravation of accompanying neurological symptoms, and may lead to severe nervous system sequelae such as subacute combined degeneration of the spinal cord. Where it is desirable to start therapy immediately, combined treatment for both deficiencies may be started once suitable samples have been taken to permit diagnosis of the deficiency, and the patient converted to the appropriate treatment once the cause of the anaemia is known.

Vitamin B_{12} deficiency anaemia. Vitamin B_{12} deficiency and its associated symptoms may be due to malabsorption (including following gastrectomy), dietary deficiency (mainly in strict vegetarians), competition with intestinal bacteria or parasites, or to the effect of drugs such as nitrous oxide. In populations of northern European origin, pernicious anaemia, in which atrophy of the gastric mucosa results in a lack of the intrinsic factor essential for B_{12} absorption, is the most frequent cause. As body stores of the vitamin are large, it may take several years for signs of deficiency to manifest once the defect in absorption occurs.

In addition to megaloblastic anaemia, vitamin B_{12} deficiency may result in neurological damage, including peripheral neuropathy and effects on mental function ranging from mild neurosis to dementia.

Treatment. The treatment is with vitamin B_{12}, almost always by the intramuscular or sometimes the deep subcutaneous route since in most patients absorption from the gastrointestinal tract is inadequate. Hydroxocobalamin is generally preferred to cyanocobalamin since it need be given less often. Regimens may vary, but hydroxocobalamin 1 mg every few days for 6 doses will restore normal body stores of the vitamin (see also Uses and Administration, above). Dosage has not been well established in children; the *BNFC* recommends similar doses to those licensed in adults. The haematological response to therapy is rapid, with improvement in most parameters and symptoms beginning within 48 hours. Neurological abnormalities may take much longer to respond, and may not do so completely.

PROPHYLAXIS. Where the defect in B_{12} handling is irreversible, as in pernicious anaemia, maintenance therapy must continue for life to prevent a recurrence of the deficiency. Therapy must also be given prophylactically after total gastrectomy or total ileal resection, or where gastrointestinal surgery is shown to have impaired absorption of the vitamin. Typically, injection of hydroxocobalamin 1 mg every 3 months is used. In patients whose diet supplies inadequate B_{12}, deficiency may be prevented, in the absence of other causes, by much lower oral doses given as a supplement; up to 150 micrograms of cyanocobalamin daily has been recommended.

Folate-deficiency anaemia. Deficiency of folate may be due to inadequate diet, or malabsorption syndromes (such as coeliac disease or sprue), to increased need (as in pregnancy, one of the most common causes of megaloblastic anaemia, or the increased haematopoiesis of haemolytic syndromes), to increased urinary loss or loss due to haemodialysis, or to an adverse effect of alcohol, antiepileptics, or other drugs.

The clinical features of folate-deficient megaloblastic anaemia are similar to those of disease due to vitamin-B_{12} deficiency except that the accompanying severe neuropathy does not occur, and deficiency may develop much more rapidly. Deficiency may also be associated with neural tube defects (p.1942) if it occurs in pregnancy.

TREATMENT. Once folate deficiency has been established the usual treatment in the UK is folic acid 5 mg by mouth daily. Lower doses of up to 1 mg are suggested in the USA. It is customary to continue therapy for at least 4 months, the time necessary for complete red cell replacement. In patients with malabsorption, therapy may require higher doses, up to 15 mg of folic acid daily. As in B_{12}-deficiency anaemia, the response to therapy is rapid.

PROPHYLAXIS. Long-term maintenance is rarely needed, except in a few patients in whom the underlying cause of folate deficiency cannot be treated (for example in some severe haemolytic syndromes). Doses of 5 mg daily or even weekly have been suggested for prophylaxis in patients undergoing dialysis or with chronic haemolytic states, depending on the diet and rate of haemolysis; a dose of 400 micrograms daily is recommended in the USA.

For primary prophylaxis of megaloblastic anaemia in pregnancy, folic acid is given in the UK in usual doses of 200 to 500 micrograms daily, often with a ferrous salt for prophylaxis of iron deficiency.

Drugs that act as inhibitors of dihydrofolate reductase, such as methotrexate, may produce severe megaloblastic anaemia which cannot be reversed by therapy with folic acid. The adverse effects of such drugs may be largely prevented or reversed by therapy with folinic acid, which can be incorporated into folate metabolism without the need for reduction by the inhibited enzyme. For details of such 'folinic acid rescue', see under Folinic Acid, p.1944.

General references.

1. Wickramasinghe SN. Folate and vitamin B deficiency and supplementation. *Prescribers' J* 1997; **37:** 88–95.
2. Wickramasinghe SN. The wide spectrum and unresolved issues of megaloblastic anemia. *Semin Hematol* 1999; **36:** 3–18.
3. Rasmussen SA, *et al.* Vitamin B deficiency in children and adolescents. *J Pediatr* 2001; **138:** 10–17.
4. Hoffbrand V, Provan D. Macrocytic anaemias. In: Provan D, ed. *ABC of clinical haematology.* 2nd ed. London: BMJ Publishing Group, 2003.
5. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. *Annu Rev Nutr* 2004; **24:** 299–326.

Neural tube defects. There is abnormality in homocysteine metabolism in many women who give birth to children with neural tube defects (p.1942); the enzyme methionine synthase, which converts homocysteine to methionine, requires both folate and vitamin B_{12} as cofactors, and low maternal vitamin B_{12} concentrations may be an independent risk factor for neural tube defects.[1] A case-control study found elevated mid-trimester methylmalonic acid concentrations in women with pregnancies affected by neural tube defects, suggesting that abnormalities of cobalamin metabolism, and subsequent methylation, may be involved in the aetiology of neural tube defects.[2] Decreased vitamin B_{12} concentrations, but no folate deficiency, were found in 3 women with pregnancies affected by neural tube defects.[3] A review[4] of case-control studies found a moderate association between low maternal vitamin B_{12} status and the risk of fetal neural tube defects. If confirmed, this would suggest that additional supplementation with cobalamins may be warranted.[3-5]

1. Mills JL, *et al.* Homocysteine metabolism in pregnancies complicated by neural-tube defects. *Lancet* 1995; **345:** 149–51.
2. Adams MJ, *et al.* Elevated midtrimester serum methylmalonic acid levels as a risk factor for neural tube defects. *Teratology* 1995; **51:** 311–17.
3. Candito M, *et al.* Anomalies du tube neural et vitamine B12: à propos de trois cas. *Ann Biol Clin (Paris)* 2004; **62:** 235–8.
4. Ray JG, Blom HJ. Vitamin B12 insufficiency and the risk of fetal neural tube defects. *Q J Med* 2003; **96:** 289–95.
5. Refsum H. Folate, vitamin B12 and homocysteine in relation to birth defects and pregnancy outcome. *Br J Nutr* 2001; **85** (suppl): S109–S113.

Osteoporosis. An elevated serum homocysteine concentration appears to be a risk factor for osteoporotic fractures in older men and women.[1-3] Treatment with vitamin B_{12} and folate can reduce plasma homocysteine concentrations (see Cardiovascular Disease, under Folic Acid, p.1941). In a placebo-controlled study of patients with hemiplegia following stroke (and at increased risk of hip fracture),[4] those given folate and vitamin B_{12} were found to have a significantly reduced risk of hip fracture despite a lack of effect on bone mineral density. Vitamin B_{12} status has been associated with bone health in a number of studies,[3,5] and it was suggested that the observed effects on fracture might be due to increased concentrations of vitamin B_{12} rather than the lowering of plasma homocysteine.[3,6]

1. van Meurs JBJ, *et al.* Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med* 2004; **350:** 2033–41.
2. McLean RR, *et al.* Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med* 2004; **350:** 2042–9.
3. van Meurs JBJ, Uitterlinden AG. Homocysteine and fracture prevention. *JAMA* 2005; **293:** 1121–2.
4. Sato Y, *et al.* Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA* 2005; **293:** 1082–8. Correction. *ibid.* 2006; **296:** 396.
5. Dhonukshe-Rutten RAM, *et al.* Vitamin B-12 status is associated with bone mineral content and bone mineral density in frail elderly women but not in men. *J Nutr* 2003; **133:** 801–7.
6. Sugiyama T, *et al.* Folate and vitamin B for hip fracture prevention after stroke. *JAMA* 2005; **294:** 792.

Rhinitis. A sublingual formulation of cyanocobalamin (*PreHistin; Cobalis, USA*) has been reported to be under investigation in the management of seasonal allergic rhinitis, but published studies are lacking.

Preparations

BP 2008: Cyanocobalamin Tablets; Hydroxocobalamin Injection;
USP 31: Cyanocobalamin Injection; Hydroxocobalamin Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Benzoral†; Difenac Forte; Lisoneurin B12; Methycobal†; Reedvit†; SL B12; Vitam Doce; ***Austral.:*** Cytamen; Neo-Cytamen; ***Austria:*** Diclo-B; Erycytol; Hepavit; ***Belg.:*** Forta B†; ***Braz.:*** Bedozil; Cianon B12; Cronobe; Enzicoba; Rubranova; Vitadoze†; Zinabol†; ***Canad.:*** Bedoz†; ***Cz.:*** B Ankermann†; Neurobene; ***Denm.:*** Betolvex; Videben; ***Fin.:*** Betolvex; Cohemin; ***Fr.:*** Cobanzyme; Cyanokit; Dodecavit; Epithea; ***Ger.:*** Ambe 12; Aquo-Cytobion†; B 12-L 90†; B12 Depot-Rotexmedica; B12 Rotexmedica; B12 Steigerwald; B Ankermann; B Depot-Hevert; B Vicotrat†; B -ASmedic; Cytobion; Hamo-Vibolex†; Lophakomp-B 12; Lophakomp-B 12 Depot; Novidroxin†; Novirell B Mono; Vicapan N†; ***Gr.:*** Articlox; Idroxocobalamina†; ***Hong Kong:*** Cobamin; Cyanokit; Methycobal; ***Hung.:*** Feroglobin-B12; ***India:*** Mecovit; Methycobal; Myelogen†; ***Indon.:*** Arcored; Berthyco; Cobazim; Ethigobal; Kalmeco; Lapibal; Meconeuro; Megabal; Methycobal; Metifer; Mevrabal; Nerfeco; Neulamin; Nufacobal; Scanmecob; Sohobal; ***Irl.:*** Cytacon; Cytamen; Neo-Cytamen; ***Israel:*** Bedodeka; Bevitex; Nascobal; ***Ital.:*** Cobaforte; Dobetin; Eritrovit B12†; Indusil; Neo-Cytamen; OH B12; ***Jpn:*** Methycobal; ***Malaysia:*** Methycobal; Neuromethyn; ***Mex.:*** Axofor; Biocobal; Biotrefon L; Bissel 12; Compensal; Droxivit†; Duradoce; Exorvit; Fortical; Hidroxovit†; Leo-Doce; Maxibol; Nebal; Neribax†; Neurofor; Rubrina†; Sanovit; Selectofort†; Valamin 12†; ***Neth.:*** Hydrocobamine; ***Norw.:*** Betolvex; ***NZ:*** Neo-B12; Neo-Cytamen; ***Philipp.:*** Drexabion; Heraclene; Hybutin; Jaga; Lixtress; Mecovit; Meganerv; Methycobal; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Rubramin; Supraneuron; Vineuron; ***Port.:*** Algobaz†; Bedoze†; Co-Vibedoze; Cobamet†; Cobaxid; Dozefol; Jaba B ; OH B12; Permadoze; Tridocemine†; ***S.Afr.:*** Cobalatec; Norivite-12†; ***Singapore:*** Hidomin†; Methycobal; Neuromethyn; ***Spain:*** Asimil B12†; Cromatonbic B12; Isopto B 12; Megamilbedoce; Optovite B12; Reticulogen Fortificado†; Zimadoce; ***Swed.:*** Behepan; Betolvex; Betolvidon; ***Switz.:*** Betolvex; Vitarubin; ***Thai.:*** Ampavit; Hitocobamin; Mecobal; Merabin; Methycobal; Neuromet; Redisol†; Sicobal†; ***Turk.:*** Aktibol; Dodex; ***UAE:*** Cynovit; ***UK:*** Cobalin-H; Cytacon; Cytamen; Neo-Cytamen; ***USA:*** CaloMist; Crystamine; Crysti 1000; Cyanokit; Cyomin; Hydro Cobex; Hydro-Crysti-12; LA-12†; Nascobal; Twelve Resin-K; ***Venez.:*** Bedovit Simple; Beplus; Cristadoce; Dobetin; Docebe B12†; Droxofor†; Hidro-Doce; Ibedox; Maxibol.

Multi-ingredient: ***Arg.:*** Acifol-B12; Algio Nervomax; Algio Nervomax Fuerte; Anemidox-Ferrum; Anemidox-Solutab; Betametasona B12; Bioneural B12†; Blastop; Blokium B12; Buta Rut B12; Cobenexol Forte; Cobenexol Fuerte; Corteroid Gesic; CVP B1 B6 B12†; Dastonil; Delta Tomanil B12; Dexabion; Diclogesic Plus B12; Dioxaflex B12; Dolo Nervobion; Dolo Nervobion 10000; Dorixina B1 B6 B12; Doxtran B12; Factofer B12; Ferranin Complex; Ferrocebrina; Flexicamin B12; Flogiatrin B12; Hierro Folico; ITE B12 Forte; Klosidol B1 B6 B12; Nervobion Fuerte; Nervomax TB12; Nucleo CMP†; Oxa B12; Presterin; QX 10; Rodinac B12; Rubiron; Siderblut Folic; Sindrolen†; Tenvic; Tunik B12; Vesalion B12; Virobron B12 NF; Vitalix Complex; Xedenol B12; Yectafer Complex; ***Austral.:*** Medinat PMT-Eze†; ***Austria:*** Ambene; Ambene N; Arca-Be; Beneuran compositum; Diclovit; Neurobion; Neuromerck; Neuromultivit; Pronerv; Rheumesser; ***Belg.:*** Neurobion; Vioneurin†; ***Braz.:*** Aminocid†; Anemofer†; Bicavine; Calcifix B12; Calcinol Complexo; Cianotrat-Dexa; Citoneurin; Cobactin; Cobaglobal; Cobavit; Cobavital; Corabent†; Dexa-Citoneurin; Dexa-Cronobe; Dexa-Neuriberi†; Dexacobal; Dexador; Dexadoze; Dexagil; Dexalgen; Dexaneurin; Dexanevral†; Dozeneurin; Ferroplex; Ferrotrat; Fol Sang; Hematiase B12; Hepatotris†; Iloban; Lisan†; Lisotox; Metiocolin B12; Metiocolin Composto; Nucleo CMP; Tirubin†; Vi-Ferrin; Vitaneuron†; Vitatonus; Xantinon Complex; ***Canad.:*** Acti-B ; Fortiplex†; Penta-3B; Penta-3B + C; ***Chile:*** Betonvit†; Citoneuron; Cronoferril†; Dolotol 12; Ferranem; Ferranim; Foli Doce; Folifer; Nefersil B; Neurobionta; Neurocam; Tol 12; Tol 12 Plus; ***Cz.:*** Aktiferrin Compositum; Dicopac†; Ferro-Folgamma; Milgamma; Milgamma N; Neuromultivit; ***Fin.:*** Neurobion; Neurovitan; ***Ger.:*** Ambene Comp†; B-Komplex forte; B Fol-Vicotrat†; Dolo-Neurobion forte†; Eryfer comp; Eukalisan N; Ferro sanol comp; Ferro-Folgamma; Folgamma; Hepagrisevit Forte-N†; Medivitan N; Medyn; Milgamma N; Neuro-ratiopharm†; Neurobion; NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; Selectafer N†; Telbibur N†; Vitaject†; Vitasprint B †; ***Gr.:*** Neurobion; ***Hong Kong:*** 3B; Neuro B1-6-12†; Neurobion; Neuromin; Neurorubine; Nevramin; Princi-B Fort; Vibion; Vida Neurotab; Vidaclofen-Plus; ***Hung.:*** Atherovit; Ferro-Folgamma; Milgamma; Milgamma N; Neurobion; ***India:*** Alcrin-M; Anemidox; Blosyn; Calcinol; Carboflot†; Conviron-TR; Delphicol; Dexorange; Elferri-Z; Ferrochelate; Fervit†; Genfol; Globac-Z; Hepasules; Hepatoglobine; Jectocos Plus; Macalvit; Omilcal; Ostocalcium B-12; Plastules; Sigmacalvit; Sioneuron; Softeron; Tonoferon; Vitamon; Vitneurin; ***Indon.:*** Abajos; Adfer; Arsinal; Betrion; Bicitron; Biocombin; Biomega; Biomex; Biosanbe; Corobion; Corsaneuron; Daneuron; Dolo Scanneuron; Dolo-Licobion; Dolo-Neurobion; Dolofenac; Farbion; Foraneural; Fundamin-E; Goralgin; Ikaneuron; Ikaneuron Plus; LaktaFit; Lapibion; Licobion; Mecola; Moloco + B12; Neogobion; Nervitone; Nervitone E; Neuralgin RX; Neuro Panstop; Neuro-Beston; Neurobat; Neurobat A; Neurobion; Neurobiovit; Neurodex; Neurohax; Neurophil; Neuropyramin; Neurosanbe; Neurosanbe Plus; Neurotrat; Neurotropic Plus; Neurovit E; Nevradin; Nevramin; Penagon; Ponconeuron; Primabion; Pritagesic; Remasal; Sangobion; Scanneuron; Sohobion; Solaneuron; Stileran; Tocobion; Trimate-E; Tropineuron; ***Israel:*** Tribemin; Tricardia; ***Ital.:*** Adenobeta†; Adenoplex; Adenovit†; Benexol B12; Briogen†; Calcio Dobetin; Co-Carnetina B12; Dobetin con Vitamina B1; Dobetin Totale; Emazian B12†; Emoantitossina†; Emopon; Epargriseovit; Eparmefolin; Fibronevrina; Folepar B12; Fosfo Plus; Fosfoutipi Vitaminico†; Gluta Complex†; Glutamin Fosforo; Hepa-Factor; Hepatos B12; Memovisus†; Memovit B12; Mionevrasi; Neo-Eparbiol†; Neuraben; Porfirin 12; Tonogen; Tricortin; Trinevrina B6; Vitasprint Complex†; Vitasprint†; ***Jpn:*** Neurovitan†; ***Malaysia:*** 3B; Alinamin B12†; Ferrovit; Flavettes Neuroforte; Fundamin-E; Neuro B†; Neurobion; Neurorubine; Neurovit†; Nevramin; Princi-B Fort; Re-B; Sangobion; Vitabion; ***Mex.:*** Ariflam Forte; B1-12-15; Bedoce-Cal; Bedocil†; Benexol B12; Betrox; Ciprolisina; Cobotiaxina; Dexabion; Diclovith-B; Dodemina Tri; Dolo-Neurobion; Dolo-Pangavit; Dolo-Tiaminal; Doxemina; Duciclon; Forvin; Gonakor; Innobion; Intrafer F-800; Iodarsolo B12†; Macrox-5; Milbeta; Neuralin; Neurobion; Neuroflax; Nuro-B; Odexan; Orafer Comp; Pangavit B; Pangavit Hypak; Pangavit Pediatrico; Revitaliv-C; Selectadoce; Suma-B; Tiabexol; Tiamidexal; Tiaminal B ; Tiaminal B Trivalente; Tribedoce; Tribedoce Compuesto; Tribedoxyl†; Trineurovita; Trineurovita Compuesto; Uni-Dox; ***Neth.:*** Neurobion; ***Philipp.:*** Beniforte; Dolo-Neurobion; Essenfer; Glutaphos; Godex; Harvifer; Hinuron-E; Meganerv F-A; Neuroforte-E; Nevramin; Nuron-E; Osteo-4; Sangobion; TriHEMIC; Vitanerv; ***Pol.:*** Additiva Ferrum; Milgamma N; Vegevit B ; ***Port.:*** Linamin Plus†; Neobefol; Neurobion; ***Rus.:*** Ambene (Амбене); Ferro-Folgamma (Феррo-Фольгамма); Milgamma (Мильгамма); Neuromultivit (Нейромультивит); ***S.Afr.:*** Foliglobin; Neurobion; Prohep; Sentinel Ulcer Mixture; ***Singapore:*** Aktiferrin-F; Alinamin B12†; Daneuron; Iron Melts; Neogobion; Neurobion; Neurodex; Neuroforte; Neurorubine; Neurovit; Neuroxel; Nevramin; Princi-B Fort; Sangobion; Wanse; ***Spain:*** Antineurina; Benexol B1 B6 B12; Bester Complex; Calcio 20 Complex; Covitasa B12; Dalamon†; Duplicalcio B12; Enoton; Foli Doce; Hepa Factor; Hidroxil B12 B6 B1; Inzitan; Malandil; Mederebro; Menalgil B6; Nervobion; Neuromade; Neurostop Complex; Refulgin; Rubrocortin†; Taurobetina†; Tonico Juventus; Trofalgon; Viadetres†; Vitafardi C B12; ***Swed.:*** Neurobion; ***Switz.:*** Benexol B12; Neurorubin; Trilagavit; Vitasprint Complex; ***Thai.:*** 3B; Alinamin B12†; Beromin; Cydoxmine-B†; Cyriamine; Douzabox; Genavit; Hemolax; Neubee; Neurobex; Neurobion; Nevramin; Nuro-B; Nuvit; Ostone-B12; Princi-B; Re-B Forte; Trabit†; Tribesian; Tricortin†; Trinsicon†; Trivit-B; Vita-B; Vitabion; Vitamedin†; Vitron; ***Turk.:*** Blood Builder; Epargriseovit; Neurogriseovit; Tribeksol; ***UAE:*** 3V; ***UK:*** Dicopac; Hematinic; ***USA:*** Anemagen†; Bevitamel; Cerefolin; Chromagen; Chromagen FA; Chromagen Forte; Contrin; Fe-Tinic Forte; FeoGen; Ferotrinsic; Ferralet Plus†; Ferrex Forte; Ferrex Forte Plus†; Ferrogels Forte; Fetrin; FOLTX; Fumatinic; Hem Fe; Hemocyte-F; Icar-C Plus; Livitrinsic-f; Metanx; Niferex Forte; Poly-Iron Forte; PremesisRx; Pronemia Hematinic; Tolfinic; TriHEMIC; Trinsicon; ***Venez.:*** Autrin†; Bedoyecta; Beferron; Befosfin; Briomet; Cianofer; Cobalfer; Deca-Lentermina Complex; Dobetin Compuesto; Fefol; Fercobre B-12†; Fercor†; Ferroce con B12; Folifer B-12; Hepafol; Hepafol con B-12; Intafer; Lentermina Complex; Mega-Neubion; Miovit; Neubion; Neuribe; Rubrinal; Rubrinex; Tres-Be.

Vitamin C Substances

Vitamina C.

Several substances have vitamin C activity, notably ascorbic acid and its calcium and sodium salts. Natural products with a high vitamin C content include black currant (p.2267), lemon (p.2332), sweet orange (p.2357), and rose fruit (p.2381).

Ascorbic Acid *(BAN, rINN)*

Acide ascorbique; Ácido ascórbico; Acidum ascorbicum; L-Ascorbic Acid; Askorbiinihappo; Askorbik Asit; Askorbinsyra; Askorbo rūgštis; Aszkorbinsav; Cevitamic Acid; E300; Kwas askorbowy; Kyselina askorbová; Vitamin C. The enolic form of 3-oxo-L-gulofuranolactone; 2,3-Didehydro-L-*threo*-hexono-1,4-lactone.

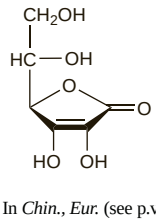
Аскорбиновая кислота

$C_6H_8O_6$ = 176.1.

CAS — 50-81-7.

ATC — A11GA01; G01AD03; S01XA15.

ATC Vet — QA11GA01; QG01AD03; QS01XA15.



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

Ph. Eur. 6.2 (Ascorbic Acid). A white or almost white crystalline powder or colourless crystals becoming discoloured on exposure to air and moisture. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 2.1 to 2.6. Store in nonmetallic containers. Protect from light.

USP 31 (Ascorbic Acid). White or slightly yellow crystals or powder. On exposure to light, it gradually darkens. In the dry state, is reasonably stable in air, but in solution rapidly oxidises. Soluble 1 in 3 of water and 1 in 40 of alcohol; insoluble in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.