

PROPHYLAXIS. Where the defect in B₁₂ 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 B₁₂, 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-B₁₂ 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 B₁₂-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 folic acid, which can be incorporated into folate metabolism without the need for reduction by the inhibited enzyme. For details of such 'folic acid rescue', see under Folic Acid, p.1944.

General references.

- Wickramasinghe SN. Folate and vitamin B₁₂ deficiency and supplementation. *Prescribers' J* 1997; **37**: 88–95.
- Wickramasinghe SN. The wide spectrum and unresolved issues of megaloblastic anemia. *Semin Hematol* 1999; **36**: 3–18.
- Rasmussen SA, et al. Vitamin B₁₂ deficiency in children and adolescents. *J Pediatr* 2001; **138**: 10–17.
- Hoffbrand V, Provan D. Macrocytic anaemias. In: Provan D, ed. *ABC of clinical haematology*. 2nd ed. London: BMJ Publishing Group, 2003.
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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 B₁₂ as cofactors, and low maternal vitamin B₁₂ 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 B₁₂ concentrations, but no folate deficiency, were found in 3 women with pregnancies affected by neural tube defects.³ A review⁴ of case-control studies found a moderate association between low maternal vitamin B₁₂ status and the risk of fetal neural tube defects. If confirmed, this would suggest that additional supplementation with cobalamins may be warranted.^{3,5}

- Mills JL, et al. Homocysteine metabolism in pregnancies complicated by neural-tube defects. *Lancet* 1995; **345**: 149–51.
- Adams MJ, et al. Elevated midtrimester serum methylmalonic acid levels as a risk factor for neural tube defects. *Teratology* 1995; **51**: 311–17.
- Candito M, et al. Anomalies du tube neural et vitamine B₁₂: à propos de trois cas. *Ann Biol Clin (Paris)* 2004; **62**: 235–8.
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- 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 B₁₂ 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 B₁₂ were found to have a significantly reduced risk of hip fracture despite a lack of effect on bone mineral density. Vitamin B₁₂ 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 B₁₂ rather than the lowering of plasma homocysteine.^{3,6}

- van Meurs JBJ, et al. Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med* 2004; **350**: 2033–41.
- McLean RR, et al. Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med* 2004; **350**: 2042–9.
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- Dhondushe-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.
- Sugiyama T, et al. Folate and vitamin B₁₂ 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; Reeditvit; SL B12; Vitam Doce; **Austral:** Cytamen; Neo-Cytamen; **Austria:** Dicl-B; Erycytol; Hepavit; **Belg:** Forta B; **Braz:** Bedozil; Canon B12; Cronob; Enzicob; Rubranova; Vitadoze; Zinobal; **Canad:** Bedoz; **Cz:** B. Ankermann; **Neurobex:** **Denm:** Betolox; **Vibed:** **Fin:** Betolox; **Cohem:** **Fr:** Cobanzyme; **Cyanokit:** Dodecavit; **Epitha:** **Ger:** Ambe 12; Aquo-Cytobion; B 12-L 90; B12 Depot-Rotexmedica; B12 Rotexmedica; B12 Steigerwald; B. Ankermann; B. Depot-Hevert; B. Vitacort; B. -AS-med; Cytobion; Hemo-Vibex; Lophakomp-B 12; Lophakomp-B 12 Depot; Novidroxin; Novirell B Mono; Vicanap N; **Gr:** Artidox; Idroxocobalamin; **Hong Kong:** Cobamin; **Cyanokit:** Methycobal; **Hung:** Ferroglobin-B12; **India:** Mecovit; Methycobal; Myelogen; **Indon:** Arcored; Berthyc; Cobazim; Ethigobal; Kalmeco; Lipabal; Meconeuro; Megabal; Methycobal; Metifer; Mervabal; Nerfeco; Neulamin; Nufacobal; Scannecob; Sohobal; **Irl:** Cytacen; 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; Biotrofen L; Bissel 12; Compensal; Droxivit; Duradoce; Exorvit; Fortical; Hidroxovit; Leo-Doce; Maxibol; Nebal; Neribax; Neurofor; Rubrina; Sanovit; Selectofort; Valamin 12; **Neth:** Hydrocobamine; **Norw:** Betolox; **NZ:** Neo-B12; Neo-Cytamen; **Philipp:** Drexabion; Rubramin; Supraneuron; Vneuron; **Port:** Algobaz; Bedoze; Co-Vibedox; Cobamet; Cobaxid; Dozefol; Jaba B ; OH B12; Permadoxe; Tridocemine; **S.Afr:** Cobalatec; Norvite-12; **Singapore:** Hidomin; Methycobal; Neuromethyn; **Spain:** Assim B12; Cromatonic B12; Isopto B 12; Megamilbedoxe; Optovite B12; Reticolugon Fortificado; Zimadoce; **Swed:** Behepan; Betolox; Betolvidon; **Switz:** Betolox; Vitabion; **Thai:** Ampavit; Hitocobamin; Mecobal; Merabin; Methycobal; Neuromet; Redisof; Sicobal; **Turk:** Aktibol; Dodox; **UAE:** Cynovit; **UK:** Cobalin-H; Cytacen; Cytamen; Neo-Cytamen; **USA:** Calomist; Crystamine; Crysti 1000; **Cyanokit:** Cytamin; Hydro Cobex; Hydro-Crysti-12; LA-12; Nascobal; Twelve Resin-K; **Venez:** Bedovit Simple; Bepus; Crastodex; Dobetin; Docebe B12; Droxofort; Hidro-Doce; Ibedox; Maxibol.

Multi-ingredient: **Arg:** Acifol-B12; Algio Nervomax; Algio Nervomax Forte; Anemidox-Ferrum; Anemidox-Solutab; Betametasona B12; Bioneural B12; Blastop; Blokium B12; Buta Rut B12; Cobenexol Forte; Cobenexol Forte; Cortoides Gestic; CVP B1 B6 B12; Dastolin; Delta Tomanil B12; Dexabion; Dilogestic Plus B12; Dioxaflex B12; Dolo Nervobion; Dolo Nervobion 10000; Dorxina B1 B6 B12; Doxtran B12; Factofor B12; Ferranin Complex; Ferrocobrin; Flexicamin B12; Florigatin B12; Hlerro Folico; ITE B12 Forte; Kisodil B1 B6 B12; Nervobion Forte; Nervomax TB12; Nucleo CMP; Oxa B12; Presterin; QX 10; Rodinac B12; Rubiron; Siderblut Folic; Sindrolin; Tervic; Tunik B12; Vesalion B12; Virobron B12 NF; Vitalex Complex; Xedenol B12; Yectafar Complex; **Austral:** Medinat PMT-Eze; **Austria:** Ambene; Ambene N; Arca-B6; Beneran composum; Didovit; Neurobion; Neuromer; Neuromultivit; Pronerv; Rheumesser; **Belg:** Neurobion; Vioneurin; **Braz:** Aminocid; Anemoferr; Bicavine; Calcif B12; Calcinal Complex; Cianoat-Dexa; Citoneurin; Cobactin; Cobaglobal; Cobavit; Cobavital; Corabent; Dexa-Citoneurin; Dexa-Cronobex; Dexa-Neuribent; Dexacobal; Dexamor; Dexadoze; Dexamol; Dexamgen; Dexaneurin; Dexaneural; Dozeneurin; Ferroplex; Ferrotrat; Fol Sang; Hematiase B12; Hepatotris; Iloban; Lisant; Lisotex; Metiocolin B12; Metiocolin Composto; Nucleo CMP; Trirubint; Vi-Ferrin; Vitaneuron; Vitatonus; Xantion Complex; **Canad:** Acti-B ; Fortiplex; Penta-3B; Penta-3B + C; **Chile:** Betonvit; Citoneuron; Cronoferril; Dolotol 12; Ferranin; Ferranin; Foli Doce; Follifer; Nefersil B; Neurobionta; Neurocam; Tol 12; Tol 12 Plus; **Cz:** Aktiferrin Compositum; Dicopac; Ferro-Folgamma; Milgamma; Milgamma N; Neuromultivit; **Fin:** Neurobion; Neurovit; **Ger:** Ambene Comp; B-Komplex forte; B. Fol-Vicotrat; Dolo-Neurobion forte; Eryfer comp; Eukalan N; Ferro sanol comp; Ferro-Folgamma; Milgamma; Hepagrisvit Forte-N; Medivitan N; Medyn; Milgamma N; Neuro-ratiopharm; Neurobion; NeyNormin N (Revitorgan-Dilutionen N Nr 65); NeyTumorin N (Revitorgan-Dilutionen N Nr 66); Selectafar N; Telibur N; Vitaject; Vitaspint B ; **Gr:** Neurobion; **Hong Kong:** 3B; Neuro B1-6-12; Neurobion; Neuromin; Neurobion; Nevramin; Princi-B Fort; Vibi-on; Vida Neurotab; Vidaclofen-Plus; **Hung:** Athervit; Ferro-Folgamma; Milgamma; Milgamma N; Neurobion; **India:** Alcin-M; Anemidox; Blosyn; Calcini; Carbollit; Conviron-TR; Delphicol; Dexamor; Effern-Z; Ferrochelate; Ferrvit; Genfol; Globac-Z; Hepasules; Hepatoglobine; Jectoc Plus; Macalvit; Omical; Ostocalcium B-12; Plastules; Sigmacalvit; Sioneuron; Softon; Tonerofon; Vitamon; Vitneurin; **Indon:** Abajox; Adfer; Arsinat; Betriox; Bictrox; Biocombin; Biomega; Biomec; Biosan; Corbion; Cor-saneuron; Daneuron; Dolo Scanneuron; Dolo-Licobion; Dolo-Neurobion; Dolofenac; Faneur; Foraneural; Fundamin-E; Goralgin; Ikanuron; Ikanuron Plus; Lakfit; 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; Priritage; Remasal; Sangobion; Scanneuron; Sobobion; Solaneuron; Sileran; Tocobion; Trimate-E; Tripeuron; **Israel:** Tribemint; Tricardia; **Ital:** Adenobeta; Adenoplex; Adenovit; Benexin B12; Briogen; Calcio Dobetin; Co-Carnetina B12; Dobetin con Vitamina B1; Dobetin Totale; Emazian B12; Emantofossina; Emopon; Epargrisovit; Epamefolin; Fibronevina; Folepar B12; Fosfo Plus; Fosfotipi Vitaminico; Gluta Complex; Glutamin Fosforo; Hepar-Factor; Hepatos B12; Memovis; Memovit B12; Mionevras; Neo-Eparbiol; Neuran; Porfirin 12; Tonogon; Tricortin; Trinevina B6; Vitaspint Complex; Vitaspint; **Jpn:** Neurovit; **Malaysia:** 3B; Alaminin B12; Ferrovit; Flavettes Neuroforte; Fundamin-E; Neuro B; Neurobion; Neurobion; Neurovit; Nevramin; Princi-B Fort; Re-B; Sangobion; Vitabion; **Mex:** Aniflam Forte; B1-12-15; Bedoce-Cal; Bedocil; Benexol B12; Bexox; Ciprolisina; Cobotaxina; Dexabion; Didovit-B; Dodekina Tri; Dolo-Neurobion; Dolo-Pangavit; Dolo-Taminal; Doremia; Ducilon; Forvin; Gonakor; Innobion; Intrafer F-800; Iodarsolo B12; Macro-S; Milbeta; Neuralin; Neurobion; Neuroflax; Nuro-B; Odexan; Orader Comp; Pangavit B; Pangavit Hypak; Pangavit Pediatric; Revital-C; Selectadex; Suma-B; Tabexol; Tiamidexal; Tiaminal B ; Tiaminal B Trivalente; Tribedoxe; Tribedoxe Composto; Tribedoxyl; Trineurovita; Trineurovita Composto; Tri-Dox; **Neth:** Neurobion; **Philipp:** Beniforte; Dolo-Neurobion; Essenfer; Glutaphos; Godex; Harvifer; Hinuron-E; Meganery F-A; Neuroforte-E; Nevramin; Nuron-E; Osteo-4; Sangobion; Tri-HEMIC; Vitaneur; **Pol:** Additiva Ferrum; Milgamma N; Vegetiv B ; **Port:** Linamin Plus; Neobefol; Neurobion; **Rus:** Ambene (Амбене); Ferro-Folgamma (Ферро-Фольгамма); Milgamma (Мильгамма); Neuromultivit (Нейромультивит); **S.Afr:** Foliobion; Neurobion; Prohep; Sentinel Ulcer Mixture; **Singapore:** Aktiferrin-F; Alaminin B12; Daneuron; In Melts; Neogobion; Neurobion; Neurodex; Neuroforte; Neurobion; Neurovit; Neuroxol; Nevramin; Princi-B Fort; Sangobion; Wanse; **Spain:** Antineurina; Benexol B1 B6 B12; Bester Complex; Calcio 20 Complex; Covitasa B12; Dalamon; Duplicacio B12; Enoton; Foli Doce; Hepar Factor; Hidroxil B12 B1; Inzitan; Mandalid; Mederebro; Menalgi B6; Nervobion; Neuromade; Neurostop Complex; Refulgin; Rubrocortin; Taurobetin; Tonico Juvenis; Trofalon; Viadretes; Vitafardi C B12; **Swed:** Neurobion; **Switz:** Benexol B12; Neurobion; Trilavag; Vitaspint Complex; **Thai:** 3B; Alaminin B12; Beromin; Cydoxime-F; Cyriamine; Douzabox; Genavit; Hemolax; Neubebe; Neurobex; Neurobion; Nevramin; Nuro-B; Nuvi; Ostone-B12; Princi-B; Re-B Fort; Trahit; Tribesian; Tricortin; Trinsicon; Trivit-B; Vita-B; Vitabion; Vitamedin; Vitron; **Turk:** Blood Builder; Epargrisovit; Neurogisevit; Tribeksol; **UAE:** 3V; **UK:** Dicopac; Hematinic; **USA:** Anemagen; Bevitame; Cerefolin; Chromagen; Chromagen FA; Chromagen Forte; Contrin; Fe-Tinic Forte; Fegogen; Ferrotrinsic; Ferralet Plus; Ferrex Forte; Ferrex Forte Plus; Ferrogels Forte; Fetrin; FOLT; Fumatonic; Hem Fe; Hemocyte-F; Icar-C Plus; Livitric-sic-F; Metan; Niferex Forte; Poly-Iron Forte; PremesisR; Pronemia Hematinic; Tolfirnic; Tri-HEMIC; Trinsic; **Venez:** Autrin; Bedoceta; Beferron; Befoslin; Briomet; Cianofer; Cobalfer; Deca-Lentemina Complex; Dobetin Composto; Fefol; Fercobex B-12; Fercor; Ferroc con B12; Foller B-12; Heparol; Heparol con B-12; Intafar; Lentemina Complex; Mega-Neubion; Miovit; Neubion; Neurbie; Rubrial; Rubrinex; Tres-Bex.

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; Askorbinihappo; Askorbik Asit; Askorbinsyra; Askorbo rūgštis; Askorbinsav; 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.

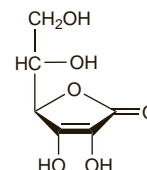
Аскорбиновая кислота

C₆H₈O₆ = 176.1.

CAS — 50-81-7.

ATC — A11GA01; G01AD03; S01XA15.

ATC Vet — Q11GA01; 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.

The symbol † denotes a preparation no longer actively marketed