Fero-Gradumet; Tardyferon; ***Swed.:*** Duroferon; ***Switz.:*** Actiferrine; Ferro-Gradumet; Resoferon†; ***Thai.:*** Fer-In-Sol; Ferrotabs; Pediron; ***Turk.:*** Oroferon; Tardyferon; ***UAE:*** Kdiron; ***UK:*** Feospan; Ferrograd; Ferrograd C; Ironorm; Slow-Fe†; ***USA:*** Ed-in-Sol†; Fe ; Feosol; Fer-gen-sol; Fer-In-Sol; Fer-Iron†; Feratab; Fero-Grad; Irospan; Slow-Fe; ***Venez.:*** Corsafer†; Fer-In-Sol; Gotafer†; Ironcor†; Mol-Iron†.

Multi-ingredient: ***Arg.:*** Factofer B12; Fefol; Ferro Folic; Hierro Plus; Iberol; Rubiron; Sideralce; Vifortol Prenatal; ***Austral.:*** Fefol; FGF Tabs; Irontona; ***Austria:*** Aktiferrin Compositum; Ferrograd Fol; Ferrum-Quarz; Kephalodoron; Tardyferon-Fol; ***Braz.:*** Anemix†; Anemofer†; Betozone; Cobaldoze; Combiron; Coraben†; Dobiron; Ferrocomplex; Ferroplex; Ferrotonico B12†; Ferrotonico†; Ferrotrat; Iberin Folico; Iberol; Novofer; Paratonico; Rubrargil; Sulfato Ferroso Composto; Sulfatofer†; Tonico Blumen†; ***Canad.:*** Iberet†; Slow-Fe Folic; ***Chile:*** Acomir con hierro; Ferranem; Ferro F-500 Gradumet†; Iberol; Iberol Folico; ***Cz.:*** Aktiferrin Compositum; Ferro-Folgamma; Ferrograd Folic†; Tardyferon-Fol; ***Fr.:*** Tardyferon; Tardyferon B ; ***Ger.:*** Biovital Aktiv†; Eisenkapseln†; Eryfer comp; Ferro-Folgamma; Ferro-Folsan; Hamatopan F; Kendural-Fol-500; Plastulen N; Tardyferon-Fol; ***Gr.:*** Feofol; Fero-Folic; Gyno-Tardyferon; ***Hong Kong:*** Iberet; Iberet-Folic; ***Hung.:*** Biovital†; Ferro-Folgamma; Ferrograd Folic; Tardyferon-Fol; ***India:*** Cofol; Conviron-TR; Fefol; Fefol-Z; Ferrochelate-Z; Fesovit; Iberol; JP Tone-TR; Maxiferon; Plastules; ***Indon.:*** Iberet; Iberet-Folic; ***Irl.:*** Fefol; Ferrograd Folic; Ferrotab†; ***Israel:*** Aktiferrin-F; Ferrograd Folic; Slow-Fe Folic; ***Ital.:*** Ferrograd Folic; ***Malaysia:*** Aktiferrin-F; Iberet-Folic; Iberet†; ***Mex.:*** Ferro Folico; Iberet; Iberol; Orafer Comp; Tardyferon-Fol; ***NZ:*** Ferrograd Folic; ***Philipp.:*** Ameciron; Appebon with Iron; Appetason; Drexabion OB; Dupharon; Femina; Ferlin; Ferosal; Ferro-Folsan Plus; Foralivit; IBC; Iberet; Iberet-Folic; Imefer; Irobon; Magniferron; Mediferron-Vita; Micron-C; Molvite with Iron; Propan with Iron; Regeron-E Plus; Terraferron; ***Pol.:*** Ferrograd Folic; Hemofer F; Tardyferon-Fol; ***Port.:*** Ferro-Folsan†; Ferrograd Folico; Folifer; Tardyferon-Fol; ***Rus.:*** Aktiferrin Compositum (Актиферрин Композитум); Fenules (Фенюльс); Ferro-Folgamma (Ферро-Фольгамма); Gyno-Tardyferon (Гино-тардиферон); ***S.Afr.:*** Fefol; Fefol-Vit; Fero-Folic; Ferrous Sulphate Compound; Foliglobin; ***Singapore:*** Aktiferrin-F; Ferbeaplex; Iberet; Iberet-Folic; Tardyferon B †; ***Switz.:*** Actiferrine-F Nouvelle formule; Fero-Folic; Gyno-Tardyferon; Kendural; Tardyferon; ***Thai.:*** Iberet†; ***Turk.:*** Gyno-Tardyferon; Gynoferon; Natabec; ***UAE:*** Folicron; ***UK:*** Fefol; Ferrograd Folic; Ironorm; Slow-Fe Folic†; ***USA:*** Aqua Ban Plus; Fero-Folic; Generet; Gerivites†; Iberet-Folic†; Iberet†; Slow Fe with Folic Acid; ***Venez.:*** Autrin†; Ferro-Folic; Ferroce con B12.

Ferrous Tartrate

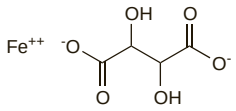
Ferrosi Tartras; Ferroso, tartrato.

$C_4H_4FeO_6,2H_2O$ = 249.0.

CAS — 2944-65-2 (anhydrous ferrous tartrate).

ATC — B03AA08.

ATC Vet — QB03AA08.



(anhydrous ferrous tartrate)

Profile

Ferrous tartrate has been used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Denm.:*** Ferroplex-frangula.

Ferumoxytol *(USAN)*

Code 7228.

Ферумокситол

CAS — 1309-38-2.

Profile

Ferumoxytol is a superparamagnetic iron oxide that is coated with a low-molecular-weight semisynthetic carbohydrate, polyglucose sorbitol carboxymethyl ether. It is under investigation as a source of iron for iron-deficiency anaemia in patients with chronic kidney disease. Ferumoxytol may potentially be used as a contrast medium in magnetic resonance imaging (p.1474).

◊ References.

1. Landry R, *et al.* Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients. *Am J Nephrol* 2005; **25:** 400–10.
2. Spinowitz BS, *et al.* The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients. *Kidney Int* 2005; **68:** 1801–7.

Folic Acid *(BAN, rINN)*

Acide folique; Ácido fólico; Acidum folicum; Folacin; Folik Asit; Folinsyre; Folio rūgštis; Folsav; Folsyra; Foolihappo; Kwas foliowy; Kyselina listová; PGA; Pteroylglutamic Acid; Pteroylmonoglutamic Acid; Vitamin B_9; Vitamin B_{11}. *N*-[4-(2-Amino-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L(+)-glutamic acid.

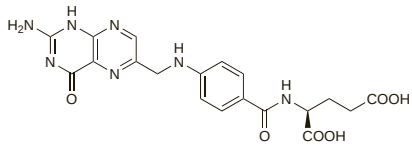
Фолиевая Кислота

$C_{19}H_{19}N_7O_6$ = 441.4.

CAS — 59-30-3 (folic acid); 6484-89-5 (sodium folate).

ATC — B03BB01.

ATC Vet — QB03BB01.



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

Ph. Eur. 6.2 (Folic Acid). A yellowish or orange crystalline powder. Practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions. Protect from light.

USP 31 (Folic Acid). A yellow, yellow-brownish, or yellowish-orange, odourless crystalline powder. Very slightly soluble in water; insoluble in alcohol, in acetone, in chloroform, and in ether. It readily dissolves in dilute solutions of alkali hydroxides and carbonates; soluble in hot, 3N hydrochloric acid and in hot, 2N sulfuric acid; soluble in hydrochloric acid and in sulfuric acid, yielding pale yellow solutions. Protect from light.

Adverse Effects

Folic acid is generally well tolerated. Gastrointestinal disturbances and hypersensitivity reactions have been reported rarely.

Hypersensitivity. A woman had 3 episodes of hypersensitivity, including anaphylaxis, on exposure to synthetic folic acid. Intradermal testing with folic acid solution was positive and a blinded challenge to folic acid solution led to widespread urticaria. Sensitisation to folic acid may have occurred after supplementation with vitamin B, at which time she had recurrent episodes of urticaria. The patient appeared to tolerate dietary folates, and the authors suggested that foods fortified with folic acid be clearly labelled.[1]

1. Smith J, *et al.* Recurrent anaphylaxis to synthetic folic acid. *Lancet* 2007; **370:** 652.

Precautions

Folic acid should never be given alone or with inadequate amounts of vitamin B_{12} for the treatment of undiagnosed megaloblastic anaemia, since folic acid may produce a haematopoietic response in patients with a megaloblastic anaemia due to vitamin B_{12} deficiency without preventing aggravation of neurological symptoms. This masking of the true deficiency state can lead to serious neurological damage, such as subacute combined degeneration of the spinal cord (see also Vitamin B_{12} Deficiency, below).

Breast feeding. Folic acid is excreted into breast milk. No adverse effects have been observed in breast-fed infants whose mothers were receiving folic acid, and the American Academy of Pediatrics considers that it is therefore usually compatible with breast feeding.[1]

1. 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 06/01/06)

Carcinogenicity. Follow-up data from a large study of folate supplementation suggested a greater risk of death due to breast cancer in those women randomised to high doses; the association was not statistically significant and further studies were considered necessary.[1] In contrast, other studies suggest a reduced risk of some cancers with folate supplementation, see Prophylaxis of Malignant Neoplasms, p.1927. A large study found that folic acid supplementation did not reduce colorectal adenoma risk; evidence for an increased risk of adenomas with supplementation was equivocal.[2] *Animal* studies suggest that folic acid may have dual modulatory effects on carcinogenesis, depending on dose and timing of supplementation. Folate deficiency may inhibit, whereas supplementation may promote, the progression of established neoplasms. In normal tissue, however, folate deficiency can predispose towards neoplastic transformation and modest amounts of folate may suppress tumour development; supraphysiological doses may enhance tumour progression.[3,4] Thus, use of folate before the existence of preneoplastic lesions may prevent tumour development, whereas use once early lesions are established appears to increase tumorigenesis.[5] However, determining the presence of preneoplastic foci in the general population is almost impossible.[4] Given the tendency for cancer patients to consume more supplements than healthy subjects, the possibility of adverse effects of folic acid on cancer progression, recurrence, and metastasis should be borne in mind, and research on folate supplementation among patients with cancer is needed.[5] Careful monitoring of the long-term effects of folic acid food fortification is also advised,[3,4] and some have advocated against mandatory fortification on this basis.[6]

1. Charles D, *et al.* Taking folate in pregnancy and risk of maternal breast cancer. *BMJ* 2004; **329:** 1375–6.
2. Cole BF, *et al.* Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 2007; **297:** 2351–9.
3. Kim Y-I. Will mandatory folic acid fortification prevent or promote cancer? *Am J Clin Nutr* 2004; **80:** 1123–8.
4. Kim Y-I. Folate: a magic bullet or a double edged sword for colorectal cancer prevention? *Gut* 2006; **55:** 1387–9.
5. Ulrich CM, Potter JD. Folate and cancer—timing is everything. *JAMA* 2007; **297:** 2408–9.
6. Hubner RA, *et al.* Should folic acid fortification be mandatory? No. *BMJ* 2007; **334:** 1253.

Vitamin B_{12} deficiency. The issue of fortification of food with folic acid to reduce the number of infants born with neural tube defects (see below) has created debate[1-7] on the amount of fortification and on the risks of masking vitamin B_{12} deficiency, particularly in the elderly. As mentioned in Precautions, above, it is accepted that folic acid should not be used in megaloblastic anaemia due to vitamin B_{12} deficiency, because it will not prevent the neurological manifestations of this deficiency, and may delay the diagnosis. Masking of vitamin B_{12} deficiency has been noted with daily doses of folic acid of 5 mg, and it is generally considered that very low doses do not have this effect. It has also been stated that folic acid may precipitate the neurological manifestations of vitamin B_{12} deficiency; however, a review of the evidence suggests this is unlikely.[8]

Nevertheless, concerns regarding neurological effects of vitamin B_{12} deficiency in the elderly have led to adoption of a level of folic acid fortification in the USA that is accepted will not provide optimum protection against neural tube defects, but that is hoped will minimise any risks.[9] It has been suggested that fortification with vitamin B_{12} as well might also be a solution.[10-12] While some studies of food fortification show no evidence of a deterioration in vitamin B_{12} status in elderly patients,[13,14] there is concern[12,15] that individuals may be consuming folic acid in excess of the upper limit of 1 mg daily (see under Human Requirements, below). Because several countries in the Americas fortify flour, but at varying levels, a technical consultation was convened by the Pan American Health Organization, the March of Dimes, and the CDC, in order to develop guidelines on fortification.[15] It was recommended[16] that all women of reproductive age consume 400 micrograms daily of synthetic folic acid in addition to dietary intake; a minimum additional intake of 200 micrograms daily of folic acid from fortified foods was proposed. A target mean intake of 1 microgram daily of vitamin B_{12} from food fortification was recommended in countries where data are consistent with vitamin B_{12} deficiency; this amount was considered sufficient since, unlike dietary sources of vitamin B_{12}, synthetic vitamin B_{12} is highly bioavailable.

1. Mills JL. Fortification of foods with folic acid—how much is enough? *N Engl J Med* 2000; **342:** 1442–5.
2. Wharton B, Booth I. Fortification of flour with folic acid: a controlled field trial is needed. *BMJ* 2001; **323:** 1198–9.
3. Wald NJ, *et al.* Quantifying the effect of folic acid. *Lancet* 2001; **358:** 2068–73. Correction. *ibid.* 2002; **359:** 630.
4. Oakley GP. Delaying folic acid fortification of flour: governments that do not ensure fortification are committing public health malpractice. *BMJ* 2002; **324:** 1348–9. Correction. *ibid.*; **325:** 259.
5. Reynolds EH. Benefits and risks of folic acid to the nervous system. *J Neurol Neurosurg Psychiatry* 2002; **72:** 567–71.
6. Shane B. Folate fortification: enough already? *Am J Clin Nutr* 2003; **77:** 8–9.
7. Wald NJ, *et al.* Vitamin B-12 and folate deficiency in elderly persons. *Am J Clin Nutr* 2004; **79:** 338.
8. Dickinson CJ. Does folic acid harm people with vitamin B deficiency? *Q J Med* 1995; **88:** 357–64.
9. Tucker KL, *et al.* Folic acid fortification of the food supply: potential benefits and risks for the elderly population. *JAMA* 1996; **276:** 1879–85. Correction. *ibid.* 1997; **277:** 714.
10. Hirsch S, *et al.* The Chilean flour folic acid fortification program reduces serum homocysteine levels and masks vitamin B-12 deficiency in elderly people. *J Nutr* 2002; **132:** 289–91.
11. Ray JG, *et al.* Persistence of vitamin B12 insufficiency among elderly women after folic acid food fortification. *Clin Biochem* 2003; **36:** 387–91.
12. Rampersaud GC, *et al.* Folate: a key to optimizing health and reducing disease risk in the elderly. *J Am Coll Nutr* 2003; **22:** 1–8.
13. Mills JL, *et al.* Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid fortification of grain. *Am J Clin Nutr* 2003; **77:** 1474–7.
14. Liu S, *et al.* A comprehensive evaluation of food fortification with folic acid for the primary prevention of neural tube defects. *BMC Pregnancy Childbirth* 2004; **4:** 20.
15. Freire WB, *et al.* Recommended levels of folic acid and vitamin B fortification: a PAHO/MOD/CDC technical consultation. *Nutr Rev* 2004; **62** (suppl): S1–S2.
16. Allen LH, *et al.* Recommended levels of folic acid and vitamin B fortification: conclusions. *Nutr Rev* 2004; **62** (suppl): S62–S66.

Interactions

Folate deficiency states may be produced by drugs such as antiepileptics, oral contraceptives, antituberculous drugs, alcohol, and folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim, and sulfonamides. In some instances, such as during methotrexate or antiepileptic therapy, replace-

ment therapy with folinic acid or folic acid may become necessary in order to prevent megaloblastic anaemia developing; folate supplementation has reportedly decreased serum-phenytoin concentrations in a few cases (see Vitamins, p.500) and there is a possibility that such an effect could also occur with barbiturate antiepileptics.

Antiepileptic-associated folate deficiency is discussed further under Effects on the Blood in Phenytoin, p.495.

◊ References.

1. Lambie DG, Johnson RH. Drugs and folate metabolism. *Drugs* 1985; **30:** 145–55.

Pharmacokinetics

Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Dietary folates are stated to have about half the bioavailability of crystalline folic acid. The naturally occurring folate polyglutamates are largely deconjugated, and then reduced by dihydrofolate reductase in the intestines to form 5-methyltetrahydrofolate, which appears in the portal circulation, where it is extensively bound to plasma proteins. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5-methyltetrahydrofolate in the plasma and liver.

The principal storage site of folate is the liver; it is also actively concentrated in the CSF.

Folate undergoes enterohepatic circulation. Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folate is distributed into breast milk. Folic acid is removed by haemodialysis.

Human Requirements

Body stores of folate in healthy persons have been reported as being between 5 to 10 mg, but may be much higher. In the UK about 150 to 200 micrograms of folate daily is considered a suitable average intake for all healthy persons except women of child-bearing potential and pregnant women who require additional folic acid to protect against neural tube defects in their offspring (see below). In the US the recommended dietary allowance is 400 micrograms of dietary folate equivalents (see below) in both men and women. Folate is present, chiefly combined with several L(+)-glutamic acid moieties, in many foods, particularly liver, kidney, yeast, and leafy green vegetables. The vitamin is readily oxidised to unavailable forms and is easily destroyed during cooking.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) have been published for folate.[1] In the USA recommended dietary allowances (RDAs) had been set, and have recently been reviewed[2] under the programme to set Dietary Reference Intakes (see p.1925). Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women. In the UK the Reference Nutrient Intake (RNI) for adult males and females is 200 micrograms daily and the Estimated Average Requirement (EAR) is 150 micrograms daily. In the USA the RDA is expressed in terms of dietary folate equivalents (DFEs) where 1 microgram DFE is equivalent to 1 microgram folate from natural sources, 0.5 micrograms of a folic acid supplement taken on an empty stomach, or 0.6 micrograms of folic acid from fortified food or as a supplement taken with meals. An RDA of 400 micrograms DFE daily for adult men and women has been set; the EAR is 320 micrograms DFE daily and the tolerable upper intake level is 1 mg daily.

Folate requirements are increased during pregnancy; an RNI of 300 micrograms daily has been suggested for pregnant women in the UK and an RDA of 600 micrograms daily in the USA. In view of the value of folate in preventing neural tube defects, it is now recommended that women planning a pregnancy receive supplemental folic acid before conception and during the first trimester (see Neural Tube Defects, below). To increase the intake in women of child-bearing age, folic acid fortification of grain-based foods has been adopted in the USA, and advocated in other countries including the UK. However, there remains some debate over the appropriate level of fortification to optimise prevention of neural tube defects and to minimise the risks of masking underlying vitamin B_{12} deficiency in the elderly (see Vitamin B_{12} deficiency, above).

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

Folic acid is a member of the vitamin B group. Folic acid is reduced in the body to tetrahydrofolate, which is a coenzyme for various metabolic processes including the synthesis of purine and pyrimidine nucleotides, and hence in the synthesis of DNA; it is also involved in some amino-acid conversions, and in the formation and utilisation of formate. Deficiency, which can result in megaloblastic anaemia (p.1982), develops when the dietary intake is inadequate (as in malnutrition), when there is malabsorption (as in sprue), increased utilisation (as in pregnancy or conditions such as haemolytic anaemia), increased loss (as in haemodialysis), or as a result of the use of folate antagonists and other drugs that interfere with normal folate metabolism (see Interactions, above).

Folic acid is used in the treatment and prevention of the folate deficiency state. It does not correct folate deficiency due to dihydrofolate reductase inhibitors; calcium folinate (p.1944) is used for this purpose. Folic acid is also used in women of child-bearing potential and pregnant women to protect against neural tube defects in their offspring. This is discussed in more detail in Neural Tube Defects, below.

For the treatment of folate-deficient megaloblastic anaemia it is recommended in the UK that folic acid is given orally in doses of 5 mg daily for 4 months; up to 15 mg daily may be necessary in malabsorption states. Continued oral dosage with folic acid 5 mg every 1 to 7 days may be necessary in chronic haemolytic states such as thalassaemia major or sickle-cell anaemia, depending on the diet and rate of haemolysis; similar doses may be necessary in some patients receiving renal dialysis in order to prevent deficiency. The *BNFC* recommends an oral dose of 500 micrograms/kg once daily for folate-dependent megaloblastic anaemia in children up to the age of 1 year; older children may be given similar doses to those in adults. For prophylaxis of folate deficiency in children on dialysis it suggests 250 micrograms/kg once daily from 1 month to 12 years of age, and 5 to 10 mg daily in older children.

In the USA the usual recommended therapeutic dose for folate deficiency is lower; oral folic acid 0.25 to 1 mg daily is suggested until a haematopoietic response has been obtained, although some patients require higher doses, especially in malabsorption states. The usual maintenance dose is 400 micrograms daily.

In the prophylaxis of megaloblastic anaemia of pregnancy, the usual dose is 200 to 500 micrograms daily in the UK.

For women of child-bearing potential at high risk of having a pregnancy affected by neural tube defect, the dose of folic acid is 4 or 5 mg daily starting before pregnancy (in the USA the recommendation is 4 weeks before) and continued through the first trimester. For other women of child-bearing potential the dose is 400 micrograms daily.

Folic acid may also be given by intramuscular, intravenous, or subcutaneous injection as the sodium salt.

Cardiovascular disease. Epidemiological studies indicate that individuals with a low serum folate are at increased risk of fatal coronary heart disease,[1] and that those with a high intake of folate,[2] or folic acid and vitamin B_6,[3] from vitamin supplements or food, are at lower risk of ischaemic heart disease or stroke. Vitamin deficiency, especially folic acid deficiency, is a common cause of hyperhomocysteinaemia.[4,5] Elevated blood-homocysteine concentrations may be an independent risk factor for atherosclerosis, ischaemic heart disease (p.1159), venous thrombosis (p.1189), and stroke (p.1185).[4-8] Whether hyperhomocysteinaemia directly causes cardiovascular disease, as concluded by a meta-analysis,[9] or is a possible marker of increased vascular risk,[10] remains controversial.[11,12]

Folic acid reduces blood-homocysteine concentrations;[13-15] vitamin B_{12}, but not B_6, may have an additional effect.[14] The higher the baseline blood-homocysteine concentration, or the lower the baseline value of folate,[14] the greater the effect of folate supplements; reductions were similar with daily doses from 0.5 to 5 mg of folic acid,[14] although a randomised trial[15] found greater effects with a daily 2-mg dose compared with a dose of 0.2 mg. A recent meta-analysis concluded that a daily dose of 0.8 mg or more was needed to achieve maximum reductions in homocysteine concentrations.[16]

Results of studies assessing cardiovascular risk versus folate intake have been variable. Although some have found the risk of hypertension,[17] or stroke[18] to be lower in patients with higher folate intakes (dietary or via supplementation), and there are suggestions that endothelial function is improved by folate supplementation,[19,20] others have reported no association between intake and cardiovascular risk.[21,22] A large open-label study[23] found that, while folic acid supplementation significantly reduced plasma homocysteine concentrations, it did not reduce recurrence of cardiovascular events in patients with stable coronary artery disease. (Most patients had been treated with lipid-lowering therapy, and the authors stated that this might have overshadowed any potential beneficial effects of folic acid.) Similarly, a randomised controlled study, the Vitamin Intervention for Stroke Prevention (VISP) trial,[24] found that high daily doses of folic acid, vitamin B_6 and vitamin B_{12} modestly decreased total homocysteine concentrations compared with low daily doses, but had no treatment effect on recurrent stroke, myocardial infarction, or death. Two further large controlled studies (HOPE-2 and NORVIT) also found no significant beneficial effect of combined treatment with folic acid and vitamins B_6 and B_{12} on cardiovascular disease risk, despite adequate homocysteine-lowering effects;[25,26] such therapy was even suggested to be harmful.[25] While one meta-analysis[27] concluded that folic acid supplementation could effectively reduce the risk of stroke in patients without a history of stroke, another[28] found no reduction in risk of cardiovascular disease, stroke, or all-cause mortality in patients with pre-existing cardiovascular or renal disease. Exclusion of the VISP study from the latter meta-analysis led to a significant protective effect of folic acid supplementation on stroke.[28]

Results of other ongoing studies are considered necessary before definite conclusions can be drawn as to the so-called 'homocysteine hypothesis' of atherothrombotic vascular disease; while some recommend against routine treatment,[4,29,30] others consider homocysteine-lowering treatment in high-risk patients to be justified.[31,32] A meta-analysis[33] of observational studies indicated that the relationship between hyperhomocysteinaemia and ischaemic heart disease and stroke risk in healthy individuals might not be as strong as had previously been suggested, with stronger associations found in retrospective studies than in prospective studies. The American Heart Association has stated[7] that, until the results of more controlled studies become available, routine testing of plasma-homocysteine concentrations cannot be justified; all patients should, however, be encouraged to consume the recommended dietary allowance (RDA) of folate, vitamin B_6 and vitamin B_{12}.

Daily treatment with oral folic acid, vitamin B_6, and vitamin B_{12} significantly decreased restenosis and target-vessel revascularisation after percutaneous coronary angioplasty.[34] In contrast, in another study[35] folic acid, vitamin B_6, and vitamin B_{12}, increased restenosis and target-vessel revascularisation. The studies differed in dosage regimen, patient population, lesion length, and procedure used,[36,37] but the strong proliferative effect of folate on neointimal growth may exceed the positive effect of lowering homocysteine concentrations,[38] and it has been stated[36] that these vitamins should not be routinely used in patients receiving coronary stents.

Patients with renal impairment develop hyperhomocysteinaemia as a result of delayed elimination and altered metabolism; the prevalence of plasma homocysteine levels greater than 15 micromoles/L has been reported to be 80 to 90% in dialysis patients, compared with 5% in the general population. In haemodialysis patients with moderate to severe hyperhomocysteinaemia, intravenous folinic acid 10 mg three times weekly has been reported to dramatically decrease homocysteine concentrations, although normal levels of homocysteine were not attained.[39] In a small study in renal transplant recipients with hyperhomocysteinaemia, vitamin B_6 was effective in reducing post-methionine-loading plasma homocysteine concentrations, and folic acid plus vitamin B_{12} was effective in lowering fasting plasma-homocysteine concentrations. The authors concluded that all three of these B-group vitamins may have a role in reducing atherosclerotic outcomes in this patient group.[40]

1. Morrison HI, *et al.* Serum folate and risk of fatal coronary heart disease. *JAMA* 1996; **275:** 1893–6.
2. Bazzano LA, *et al.* Dietary intake of folate and risk of stroke in US men and women: NHANES I Epidemiologic Follow-up Study. *Stroke* 2002; **33:** 1183–9.
3. Rimm EB, *et al.* Folate and vitamin B from diet and supplements in relation to risk of coronary heart disease among women. *JAMA* 1998; **279:** 359–64.
4. Hankey GJ, *et al.* Clinical usefulness of plasma homocysteine in vascular disease. *Med J Aust* 2004; **181:** 314–18.

5. Stanger O, *et al.* Clinical use and rational management of homocysteine, folic acid, and B vitamins in cardiovascular and thrombotic diseases. *Z Kardiol* 2004; **93:** 439–53.
6. Mangoni AA, Jackson SHD. Homocysteine and cardiovascular disease: current evidence and future prospects. *Am J Med* 2002; **112:** 556–65.
7. Malinow MR, *et al.* Homocyst(e)ine, diet, and cardiovascular diseases: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation* 1999; **99:** 178–82. Also available at: http://circ.ahajournals.org/cgi/reprint/99/1/178.pdf (accessed 06/01/06)
8. Robinson K. Homocysteine, B vitamins, and risk of cardiovascular disease. *Heart* 2000; **83:** 127–30.
9. Wald DS, *et al.* Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002; **325:** 1202–6.
10. Dusitanond P, *et al.* Homocysteine-lowering treatment with folic acid, cobalamin, and pyridoxine does not reduce blood markers of inflammation, endothelial dysfunction, or hypercoagulability in patients with previous transient ischemic attack or stroke: a randomized substudy of the VITATOPS trial. *Stroke* 2005; **36:** 144–6.
11. Doshi SN, *et al.* Lowering plasma homocysteine with folic acid in cardiovascular disease: what will the trials tell us? *Atherosclerosis* 2002; **165:** 1–3.
12. Lewis SJ, *et al.* Meta-analysis of MTHFR 677C→T polymorphism and coronary heart disease: does totality of evidence support causal role for homocysteine and preventive potential of folate? *BMJ* 2005; **331:** 1053–6.
13. Boushey CJ, *et al.* A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. *JAMA* 1995; **274:** 1049–57.
14. Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. *BMJ* 1998; **316:** 894–8.
15. PACIFIC Study Group. Dose-dependent effects of folic acid on plasma homocysteine in a randomized trial conducted among 723 individuals with coronary heart disease. *Eur Heart J* 2002; **23:** 1509–15.
16. Homocysteine Lowering Trialists' Collaboration. Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials. *Am J Clin Nutr* 2005; **82:** 806–12.
17. Forman JP, *et al.* Folate intake and the risk of incident hypertension among US women. *JAMA* 2005; **293:** 320–9.
18. He K, *et al.* Folate, vitamin B , and B intakes in relation to risk of stroke among men. *Stroke* 2004; **35:** 169–74.
19. Woo KS, *et al.* Long-term improvement in homocysteine levels and arterial endothelial function after 1-year folic acid supplementation. *Am J Med* 2002; **112:** 535–9.
20. Thambyrajah J, *et al.* A randomized double-blind placebo-controlled trial of the effect of homocysteine-lowering therapy with folic acid on endothelial function in patients with coronary artery disease. *J Am Coll Cardiol* 2001; **37:** 1858–63.
21. Al-Delaimy WK, *et al.* Folate intake and risk of stroke among women. *Stroke* 2004; **35:** 1259–63.
22. Hung J, *et al.* Folate and vitamin B-12 and risk of fatal cardiovascular disease: cohort study from Busselton, Western Australia. *BMJ* 2003; **326:** 131–4.
23. Liem A, *et al.* Secondary prevention with folic acid: effects on clinical outcomes. *J Am Coll Cardiol* 2003; **41:** 2105–13.
24. Toole JF, *et al.* Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 2004; **291:** 565–75.
25. Bønaa KH, *et al.* NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006; **354:** 1578–88.
26. Lonn E, *et al.* Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006; **354:** 1567–77.
27. Wang X, *et al.* Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. *Lancet* 2007; **369:** 1876–82.
28. Bazzano LA, *et al.* Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. *JAMA* 2006; **296:** 2720–6.
29. Hankey GJ, Eikelboom JW. Folic acid-based multivitamin therapy to prevent stroke: the jury is still out. *Stroke* 2004; **35:** 1995–8.
30. Carlsson CM. Lowering homocysteine for stroke prevention. *Lancet* 2007; **369:** 1841–2.
31. Schwammenthal Y, Tanne D. Homocysteine, B-vitamin supplementation, and stroke prevention: from observational to interventional trials. *Lancet Neurol* 2004; **3:** 493–5.
32. Wald DS, *et al.* Folic acid, homocysteine, and cardiovascular disease: judging causality in the face of inconclusive trial evidence. *BMJ* 2006; **333:** 1114–7.
33. The Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002; **288:** 2015–22.
34. Schnyder G, *et al.* Effect of homocysteine-lowering therapy with folic acid, vitamin B , and vitamin B on clinical outcome after percutaneous coronary intervention. The Swiss Heart Study: a randomized controlled trial. *JAMA* 2002; **288:** 973–9.
35. Lange H, *et al.* Folate therapy and in-stent restenosis after coronary stenting. *N Engl J Med* 2004; **350:** 2673–81.
36. Herrmann HC. Prevention of cardiovascular events after percutaneous coronary intervention. *N Engl J Med* 2004; **350:** 2708–10.
37. Stanger O, *et al.* Folate therapy and in-stent restenosis. *N Engl J Med* 2004; **351:** 1259.
38. Lange H, Suryapranata H. Folate therapy and in-stent restenosis. *N Engl J Med* 2004; **351:** 1259–60.
39. Bayés B, *et al.* 'New' cardiovascular risk factors in patients with chronic kidney disease: role of folic acid treatment. *Kidney Int* 2005; **67** (suppl 93)*:* S39–S43.
40. Bostom AG, *et al.* Treatment of hyperhomocysteinemia in renal transplant recipients. *Ann Intern Med* 1997; **127:** 1089–92.

Deficiency states. Reviews of the use of folic acid in conditions associated with folate deficiency.

1. Mason P. Folic acid—new roles for a well known vitamin. *Pharm J* 1999; **263:** 673–7.
2. Donnelly JG. Folic acid. *Crit Rev Clin Lab Sci* 2001; **38:** 183–223.
3. Stanger O. Physiology of folic acid in health and disease. *Curr Drug Metab* 2002; **3:** 211–23.
4. Paul RT, *et al.* Folic acid: neurochemistry, metabolism and relationship to depression. *Hum Psychopharmacol* 2004; **19:** 477–88.
5. Reynolds E. Vitamin B12, folic acid, and the nervous system. *Lancet Neurol* 2006; **5:** 949–60.

Food fortification. Mandatory fortification of foods with folic acid has caused much controversy, with some advocating this measure as prevention against neural tube defects (below) and others concerned about folic acid supplementation masking vitamin B_{12} deficiency (above) or having possible carcinogenic effects (above).

Further references.

1. Eichholzer M, *et al.* Folic acid: a public-health challenge. *Lancet* 2006; **367:** 1352–61.

Hearing loss. Epidemiological studies have suggested an association between homocysteine and folate concentrations and hearing status. A 3-year controlled study in a country without folic acid food fortification found that supplementation slowed the decline in age-related hearing loss. Further studies were considered necessary to confirm these findings.[1]

1. Durga J, *et al.* Effects of folic acid supplementation on hearing in older adults: a randomized, controlled trial. *Ann Intern Med* 2007; **146:** 1–9.

Mental function. For a discussion of the effects of folate supplementation on cognitive function and depression, see Mental Function, p.1926.

Neural tube defects. Failure of the fetal neural tube to fuse normally during the first 4 weeks of pregnancy may result in one of several congenital defects. These include anencephaly (absence of the brain and cranial vault) and spina bifida (failure of the vertebrae to fuse).[1,2] The latter ranges from spina bifida occulta, where neurological abnormalities are rare, to meningocoele or meningomyelocoele, where the meninges, or meninges and spinal cord, herniate outwards through the vertebral defect and which may be associated with hydrocephalus and paralysis of the lower limbs and sphincters.

The reasons for this failure in normal development are not well understood and appear to include both environmental and genetic factors. The risk is increased in certain geographical areas, and in the offspring of parents with previous children who had neural tube defects, or of parents who themselves suffer from the condition.[1]

A defect in the methylenetetrahydrofolate reductase gene has been identified, which is estimated to occur in about 5 to 15% of white populations, and appears to result in an increased requirement for folates, and an increased risk of recurrent early pregnancy loss and neural tube defects.[3,4] Since the 1960s there has been some evidence that the mother's folate status was significant, and in the early 1980s two groups published evidence for claims that oral folic acid, with or without other vitamins, in the period around conception, reduced the incidence of neural tube defect in the offspring of mothers who had previously borne children with the defect.[5,6]

Although criticised on several grounds, the conclusions of these studies were borne out by a large multicentre study initiated by the UK Medical Research Council (MRC).[7] This study was terminated early because of overwhelming evidence that folic acid 4 mg daily taken from before conception until the twelfth week of gestation by women with a history of a previous pregnancy affected by a neural tube defect reduced the incidence of such defect by about two-thirds. Other studies and systematic reviews have since confirmed the benefits of supplementation.[8,9] Multivitamins alone (A, D, B_1, B_2, nicotinamide, B_6, and C) did not demonstrate a similar benefit.

Prevention of recurrence. In the light of the MRC study, it is recommended in the UK that in couples with spina bifida or a history of previous offspring with neural tube defect, all those women who may become pregnant should receive folic acid 5 mg daily (in the absence of a commercially-available 4-mg dosage form) until the twelfth week of pregnancy.[10] In the USA, recommendations are 4 mg of folic acid daily from at least 4 weeks before conception through the first 3 months of pregnancy.[11] It must be borne in mind that only about 60 to 70% of neural tube defects appear to be folate-sensitive, and parents should be counselled appropriately. Similar doses of folic acid have been recommended for women in intermediate- to high-risk categories for neural tube defects in Canada.[12]

The investigators in the MRC trial acknowledged that a 4-mg dose may not be optimal, and both early[5,6] and later[13] studies imply that much lower doses of folic acid may reduce the risk of recurrence, but this has yet to be clearly demonstrated. Furthermore, the optimum length of time that supplements should be given to these women before conception is unknown.

Prevention of occurrence. First occurrences of neural tube defects account for about 95% of cases, and there are obvious public health implications if the benefits of folate in mothers known to be at risk can be extended to the general population. A study in Hungary[14] indicated that folic acid 800 micrograms daily with multivitamins, taken for at least one month before conception and until the third month of gestation decreased the incidence of first occurrence of neural tube defects. A case control study in the USA[15] (where the normal incidence of neural tube defect is much lower than Hungary) suggested that a periconceptional folic acid intake of as little as 400 micrograms daily reduced the occurrence of the disorder by 60%.

With such results in mind the US Public Health Service has recommended that all women of child-bearing age who are capable of pregnancy should receive folic acid 400 micrograms daily although care should be taken to keep folate consumption below 1 mg daily except under medical supervision.[1,16] Such universal coverage would allow for the problem of unplanned pregnancies but would be difficult to achieve, other than by fortification of dietary staples with folate. Food fortification has therefore been adopted in the USA, at a level of 140 micrograms of folic acid per 100 g of cereal-grain product. While this amount will probably be insufficient to provide maximum reduction in the incidence of neural tube defects,[17,18] there is some evidence of benefit,[19] and it was chosen to minimise the risk of masking vitamin B_{12} deficiency in the elderly.[20] Efforts to increase the use of folic acid supplements in women of child-bearing potential are still advocated. In Canada, where food fortification has been associated with a significant reduction in neural tube defects,[21] similar recommendations have been made.[12]

In the UK, the current recommendation is that all women planning a pregnancy should take an extra 400 micrograms of folic acid daily before conception and during the first 12 weeks of pregnancy, bringing the average folate intake to about 600 micrograms daily.[10] In unplanned pregnancies, supplementation should begin as soon as pregnancy is suspected. Some, however, consider this amount to be too low.[22] As in the USA, food fortification has been considered, and the Committee on Medical Aspects of Food and Nutrition Policy (COMA) concluded that universal fortification of flour at 240 micrograms of folic acid per 100 g in food would significantly reduce the number of neural tube defects.[23] In May 2007, the UK Food Standards Agency agreed that mandatory fortification be introduced. However, there are concerns about possible carcinogenic effects (see Carcinogenicity, above) and results of further studies are awaited. Debate has continued as to the amount, if any, of fortification necessary.[22,24-29] The UK Scientific Advisory Committee on Nutrition reconfirmed[30] the COMA recommendation for fortification of flour but said that further consideration should be given to the amount and form of folate used and also called for better monitoring of vitamin B_{12} in those aged 65 and over. There has also been a renewed call for fortification of foods in Europe,[31-34] and Australia and New Zealand,[35,36] as issuing recommendations on folic acid use has not led to a substantial decrease in the incidence of neural tube defects, and efforts have not reached all the target population. Certainly, mandatory food fortification with folic acid has been shown to dramatically decrease the incidence of neural tube defects in Canada,[37] Chile,[38] and the USA.[39-41] Fears of masking vitamin B_{12} deficiency appear to have not been borne out (see Vitamin B_{12} Deficiency, above).

Patients receiving antiepileptic drugs are at increased risk of neural tube defect and it has been suggested that folic acid supplementation for such patients should be at the level used for prevention of recurrence,[42] i.e. 4 or 5 mg daily.

The mechanism by which folic acid protects against neural tube defects is unknown, but various theories have been postulated including a positive effect in promoting neural tube closure,[43] or a selective abortifacient effect on affected fetuses (terathanasia),[44] although the latter has been disputed.[45] There is some evidence that low maternal vitamin B_{12} concentrations are an independent risk factor for neural tube defects,[46,47] perhaps indicating a role for methionine synthase in their aetiology, and suggesting that additional supplementation with cobalamins may be warranted, or that methionine supplements could be investigated as an alternative to folic acid.[48,49] Some suggest that hyperhomocysteinaemia may be a cause of some neural tube defects and that they may be due to an inborn error of folate and/or homocysteine metabolism; furthermore, a dietary deficiency may trigger a genetic predisposition towards the development of neural tube defects.[2] Interestingly, the results from the Hungarian programme[50,51] and from other studies[52-54] suggest that multivitamin supplements (including folic acid) may also reduce the occurrence of other congenital abnormalities. Maternal folate deficiency has also been associated with an increased risk of adverse birth outcomes, apart from neural tube defects, such as preterm delivery, low infant birth-weight, and fetal growth retardation.[55]

1. Botto LD, *et al.* Neural-tube defects. *N Engl J Med* 1999; **341:** 1509–19.
2. Czeizel AE. Primary prevention of neural-tube defects and some other major congenital abnormalities: recommendations for the appropriate use of folic acid during pregnancy. *Paediatr Drugs* 2000; **2:** 437–49.
3. Molloy AM, *et al.* Thermolabile variant of 5,10-methylenetetrahydrofolate reductase associated with low red-cell folates: implications for folate intake recommendations. *Lancet* 1997; **349:** 1591–3.
4. Nelen WLDM, *et al.* Recurrent early pregnancy loss and genetic-related disturbances in folate and homocysteine metabolism. *Br J Hosp Med* 1997; **58:** 511–13.
5. Smithells RW, *et al.* Apparent prevention of neural tube defects by periconceptional vitamin supplementation. *Arch Dis Child* 1981; **56:** 911–18.
6. Laurence KM, *et al.* Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural tube defects. *BMJ* 1981; **282:** 1509–11.
7. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council vitamin study. *Lancet* 1991; **338:** 131–7.

8. Berry RJ, *et al*. Prevention of neural-tube defects with folic acid in China. *N Engl J Med* 1999; **341:** 1485–90. Correction. *ibid.*; 1864.
9. Lumley J, *et al.* Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 06/01/06).
10. DoH. *Folic acid and the prevention of neural tube defects: report from an expert advisory group*. London: Department of Health, 1992.
11. CDC. Use of folic acid for prevention of spina bifida and other neural tube defects—1983-1991. *MMWR* 1991; **40:** 513–16.
12. Wilson RD, *et al*. The use of folic acid for the prevention of neural tube defects and other congenital anomalies. *J Obstet Gynaecol Can* 2003; **25:** 959–73.
13. Kirke PN, *et al.* A randomised trial of low dose folic acid to prevent neural tube defects. *Arch Dis Child* 1992; **67:** 1442–6.
14. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992; **327:** 1832–5.
15. Werler MM, *et al*. Periconceptional folic acid exposure and risk of occurrent neural tube defects. *JAMA* 1993; **269:** 1257–61.
16. CDC. Recommendations for use of folic acid to reduce number of spina bifida cases and other neural tube defects. *JAMA* 1993; **269:** 1233–8.
17. Daly S, *et al*. Minimum effective dose of folic acid for food fortification to prevent neural-tube defects. *Lancet* 1997; **350:** 1666–9.
18. Brown JE, *et al*. Predictors of red cell folate level in women attempting pregnancy. *JAMA* 1997; **277:** 548–52.
19. Honein M, *et al*. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. *JAMA* 2001; **285:** 2981–6.
20. Tucker KL, *et al*. Folic acid fortification of the food supply: potential benefits and risks for the elderly population. *JAMA* 1996; **276:** 1879–85. Correction. *ibid*. 1997; **277:** 714.
21. De Wals P, *et al*. Reduction in neural-tube defects after folic acid fortification in Canada. *N Engl J Med* 2007; **357:** 135–42.
22. Wald NJ, *et al*. Quantifying the effect of folic acid. *Lancet* 2001; **358:** 2069–73. Correction. *ibid.* 2002; **359:** 630.
23. DoH. Consultation by the UK health departments and the Food Standards Agency on the report of the Committee on Medical Aspects of Food and Nutrition Policy on folic acid and the prevention of disease. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005584?IdcService=GET_FILE&dID=12123&Rendition=Web (accessed 21/07/08)
24. Oakley GP. Delaying folic acid fortification of flour: governments that do not ensure fortification are committing public health malpractice. *BMJ* 2002; **324:** 1348–9. Correction. *ibid.*; **325:** 259.
25. Mills JL. Fortification of foods with folic acid — how much is enough? *N Engl J Med* 2000; **342:** 1442–5.
26. Wharton B, Booth I. Fortification of flour with folic acid: a controlled field trial is needed. *BMJ* 2001; **323:** 1198–9.
27. Reynolds E. Fortification of flour with folic acid: fortification has several potential risks. *BMJ* 2002; **324:** 918.
28. Wald NJ, Oakley GP. Should folic acid fortification be mandatory? Yes. *BMJ* 2007; **334:** 1252.
29. Hubner RA, *et al*. Should folic acid fortification be mandatory? No. *BMJ* 2007; **334:** 1253.
30. Scientific Advisory Committee on Nutrition. Folate and disease prevention (issued 2006). Available at: http://www.sacn.gov.uk/pdfs/folate_and_disease_prevention_report.pdf (accessed 21/07/08)
31. Botto LD, *et al*. International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working? *BMJ* 2005; **330:** 571–3.
32. Knudsen VK, *et al*. Low compliance with recommendations on folic acid use in relation to pregnancy: is there a need for fortification? *Public Health Nutr* 2004; **7:** 843–50.
33. Ali SA, Economides DL. Folic acid supplementation. *Curr Opin Obstet Gynecol* 2000; **12:** 507–12.
34. Bille C, *et al*. Folic acid and birth malformations: despite 15 years of evidence, preventable defects still occur. *BMJ* 2007; **334:** 433–4.
35. Bower C, Stanley FJ. Case for mandatory fortification of food with folate in Australia, for the prevention of neural tube defects. *Birth Defects Res A Clin Mol Teratol* 2004; **70:** 842–3.
36. Maberly GF, Stanley FJ. Mandatory fortification of flour with folic acid: an overdue public health opportunity. *Med J Aust* 2005; **183:** 342–3.
37. Liu S, *et al.* A comprehensive evaluation of food fortification with folic acid for the primary prevention of neural tube defects. *BMC Pregnancy Childbirth* 2004; **4:** 20.
38. Castilla EE, *et al*. Preliminary data on changes in neural tube defect prevalence rates after folic acid fortification in South America. *Am J Med Genet A* 2003; **123:** 123–8.
39. Honein MA, *et al.* Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. *JAMA* 2001; **285:** 2981–6.
40. CDC. Spina bifida and anencephaly before and after folic acid mandate—United States, 1995–1996 and 1999–2000. *MMWR* 2004; **53:** 362–5.
41. Mills JL, Signore C. Neural tube defect rates before and after food fortification with folic acid. *Birth Defects Res A Clin Mol Teratol* 2004; **70:** 844–5.
42. Girling JC, Shennan AH. Epilepsy and pregnancy. *BMJ* 1993; **307:** 937.
43. Zhao Q, *et al.* Prenatal folic acid treatment suppresses acrania and meroanencephaly in mice mutant for the Cart1 homeobox gene. *Nat Genet* 1996; **13:** 275–83.
44. Hook EB, Czeizel AE. Can terathanasia explain the protective effect of folic-acid supplementation on birth defects? *Lancet* 1997; **350:** 513–15.
45. Burn J, Fisk NM. Terathanasia, folic acid, and birth defects. *Lancet* 1997; **350:** 1322–3.
46. Kirke PN, *et al.* Maternal plasma folate and vitamin B are independent risk factors for neural tube defects. *Q J Med* 1993; **86:** 703–8.
47. Mills JL, *et al*. Homocysteine metabolism in pregnancies complicated by neural-tube defects. *Lancet* 1995; **345:** 149–51.
48. Klein NW. Folic acid and prevention of spina bifida. *JAMA* 1996; **275:** 1636.
49. Lewis DP, *et al*. Drug and environmental factors associated with adverse pregnancy outcomes: Part III: folic acid: pharmacology, therapeutic recommendations, and economics. *Ann Pharmacother* 1998; **32:** 1087–95.
50. Czeizel AE. Prevention of congenital abnormalities by periconceptional multivitamin supplementation. *BMJ* 1993; **306:** 1645–8.
51. Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. *Am J Med Genet* 1996; **62:** 179–83.
52. Shaw GM, *et al*. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. *Lancet* 1995; **346:** 393–6.
53. Botto LD, *et al*. Periconceptional multivitamin use and the occurrent of conotruncal heart defects: results from a population-based, case-control study. *Pediatrics* 1996; **98:** 911–17.
54. McDonald SD, *et al*. The prevention of congenital anomalies with preconceptional folic acid supplementation. *J Obstet Gynaecol Can* 2003; **25:** 115–21.
55. Scholl TO, Johnson WG. Folic acid: influence on the outcome of pregnancy. *Am J Clin Nutr* 2000; **71** (suppl): 1295S–1303S.

Osteoporosis. Treatment with folate and vitamin B_{12} can reduce elevated plasma homocysteine concentrations and may subsequently decrease the risk of osteoporosis and hip fracture, see Osteoporosis, under Vitamin B_{12}, p.1983.

Prophylaxis of malignant neoplasms. For reference to suggestions that folate supplements may be associated with reduced risk of certain cancers, see p.1927. However, folic acid may have dual modulatory effects on carcinogenesis, see Carcinogenicity, above.

Preparations

BP 2008: Ferrous Fumarate and Folic Acid Tablets; Folic Acid Tablets; ***USP 31:*** Folic Acid Injection; Folic Acid Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Acifol; Anemidox Folico; Anfolic; Azolac Folico; Biolfolic; Coflic; Conacid; Dupofol; Edulsan Folic; Egestan; Folaport; Foliagen; Folimax; Folinemic; Galfol; Livifol; Medifol; Ronfolic; Sojar Folico; Suprafol; ***Austral.:*** Megafol; ***Austria:*** Folsan; ***Belg.:*** Folavit; ***Braz.:*** Acfol†; Afopic; Endofolin; Enfol; Folacin; Folin†; Folital; Materfolic; Neo Folico; ***Chile:*** Folacid; Folifemin; Folisanin; ***Denm.:*** Folimet; ***Fin.:*** Folvite; ***Fr.:*** Speciafoldine; ***Ger.:*** DreisaFol; Fol-Asmedic†; Folarell; Folcur; Folgamma Mono; Folsan; Folverlan; Gravi-Fol; Lafol; RubieFol†; ***Gr.:*** Filicine; ***Hung.:*** Feroglobin-B12; Folsav; Huma-Folacid; ***India:*** Folet; Folvite; Ingafol; Rubraplex; Vitafol; ***Indon.:*** Folac; Folacite; Folacom; Folas; Folavit; Folaxin; Nufolic; ***Irl.:*** Cardioguard†; Clonfolic; ***Ital.:*** Fertifol; Folidex; Folina; Folingrav; Serengrav; ***Mex.:*** AF; Folivital; Materfol; Prinac Ac; ***Philipp.:*** Enhansid; Purifol; ***Pol.:*** Acifolik; Folacid; Folifem; Folik; Folimin; Folovit; ***Port.:*** Acfol; Dozefol; Folicil; ***Rus.:*** Folacin (Фолацин); ***Spain:*** Acfol; Zolico; ***Swed.:*** Folacin; ***Switz.:*** Andreafol; Drossafol; Foli-Rivo†; Folvite; ***Thai.:*** Foliamin; Folicare; Folivit; ***Turk.:*** Folbiol; ***UAE:*** Folicum; ***UK:*** Folicare; Lexpec; Preconceive; ***USA:*** Folvite; ***Venez.:*** Afoklin; Folac.

Multi-ingredient: ***Arg.:*** Acifol-B12; Anemidox-Ferrum; Anemidox-Solutab; Blastop; Egestan Hierro; Factofer B12; Fefol; Ferranin Complex; Ferretab Compuesto; Ferro Folic; Ferrocebrina; Folimax B; Hierro Dupofol; Hierro Folico; Hierro Plus; Hierroquick; ITE B12 Forte; Maltofer Fol†; Presterin; QX 10; Rubiron; Sideralce; Siderblut Folic; Tenvic; Vitalix Complex; Yectafer Complex; ***Austral.:*** Antioxidant Forte Tablets; Fefol; FGF Tabs; Pre Natal†; Vita-Preg†; ***Austria:*** Aktiferrin Compositum; Beneuran compositum; Ferretab Comp; Ferrograd Fol; Losferron-Fol; Tardyferon-Fol; ***Belg.:*** Gestiferrol; ***Braz.:*** Anemofer†; Betozone; Coraben†; Ferrini Folico; Ferroplex; Ferrotonico B12†; Ferrotrat; Ferrumvit†; Fol Sang; Folacin; Folifer; Iberin Folico; Iloban; Neutrofer Folico; Noripurum Folico; Vi-Ferrin; ***Canad.:*** Neo-Fer CF; Palafer CF; Slow-Fe Folic; ***Chile:*** Cronoferril†; Ferranem; Ferranim; Ferro F-500 Gradumet†; Ferro Vitaminico; Foli Doce; Folifer; Iberol Folico; Maltofer Fol; ***Cz.:*** Aktiferrin Compositum; Ferretab Compositum; Ferro-Folgamma; Ferrograd Folic†; Maltofer Fol; Tardyferon-Fol; ***Fin.:*** Obsidan comp; ***Fr.:*** Folio; Gynosoja; Tardyferon B ; ***Ger.:*** B Fol-Vicotrat†; Eryfer comp; Ferro sanol comp; Ferro sanol gyn; Ferro-Folgamma; Ferro-Folsan; Folgamma; Folicombin; Hamatopan F; Hepagrisevit Forte-N†; Kendural-Fol-500; Medivitan N; Medyn; MerSol†; Plastulen N; Selectafer N†; Tardyferon-Fol; ***Gr.:*** Dextrifer-Fol; Feofol; Fero-Folic; Ferrum Fol Hausmann; Gyno-Tardyferon; Hemafer fol; ***Hong Kong:*** Eurofer; Hepatofalk; Iberet-Folic; ***Hung.:*** Atherovit; Ferro-Folgamma; Ferrograd Folic; Maltofer Fol; Pregmag; Tardyferon-Fol; ***India:*** Anemidox; Blosyn; Cafe-Kit†; Carbofliot†; Cofol; Cofol Z; Conviron-TR; Dexorange; Elferri-Z; Fecontin-F; Fecontin-Z; Fefol; Fefol-Z; Fericip; Ferrochelate; Ferrochelate-Z; Fervit†; Fesovit; Genfol; Globac-Z; Hepasules; Hepatoglobine; Hepofer; Jectocos Plus; JP Tone-TR; Livogen Captab; Livogen Hemtonic; Livogen-Z; Livogen†; Maxiferon; Mumfer-Z†; Mumfer†; Plastules; Probofex; Raricap; Softeron; Softeron-Z; Tonoferon; Vitamon; ***Indon.:*** Adfer; Biosanbe; Folaplus; Hemobion; Iberet-Folic; Maltofer Fol; Natabion; Neogobion; Sangobion; Vomilat; ***Irl.:*** Fefol; Ferrocap F†; Ferrograd Folic; Galfer FA; Givitol; ***Israel:*** Aktiferrin-F; Ferrifol; Ferrograd Folic; Folex; Foric; Slow-Fe Folic; Tricardia; ***Ital.:*** Epargriseovit; Evafer; Ferrograd Folic; Folepar B12; ***Malaysia:*** Aktiferrin-F; Ferrovit; Iberet-Folic; Maltofer; Sangobion; ***Mex.:*** Dialeli AF; Ferlor AF†; Ferranina Fol; Ferricol; Ferro Folico; Forta; Intrafer; Intrafer F-800; Intrafer TF; Ironfol; Orafer Comp; Tardyferon-Fol; Uniferfol; Yemiferhe; ***NZ:*** Ferrograd Folic; ***Philipp.:*** Ameciron; Anemicon Plus; Anixon; Beniforte; Drexabion OB; Dupharon; Essenfer; Eurofer; Femina; Fergesol; Ferlin; Ferosal; Ferro-Folsan Plus; Foralivit; Foramefer; Fortifer FA; Harvifer; Hemobion; IBC; Iberet-Folic; Imefer; Irobon; Meganerv F-A; Micron-C; Molvite-OB; Nakaron; Sangobion; Terraferron; TriHEMIC; ***Pol.:*** Additiva Ferrum; Ferrograd Folic; Hemofer F; Tardyferon-Fol; ***Port.:*** Ferro-Folsan†; Ferrograd Folico; Ferrum Fol; Folifer; Maltoferfol; Neobefol; Tardyferon-Fol; ***Rus.:*** Aktiferrin Compositum (Актиферрин Композитум); Ferretab Comp (Ферретаб Комп); Ferro-Folgamma (Ферро-Фольгамма); Gyno-Tardyferon (Гино-тардиферон); ***S.Afr.:*** Fefol; Fefol-Vit; Fero-Folic; Ferrimed; Foliglobin; Hepabionta; Pregamal; ***Singapore:*** Aktiferrin-F; Eurofer; Iberet-Folic; Iron Melts; Neogobion; Saferon†; Sangobion; Tardyferon B †; Wanse; ***Spain:*** Foli Doce; Foliferron; Hepa Factor; Normovite Antianemico; ***Switz.:*** Actiferrine-F Nouvelle formule; Duofer Fol; Fero-Folic; Gyno-Tardyferon; Maltofer Fol; ***Thai.:*** Adnemic F†; Eurofer; Ferli-6; Ferosix; Orofer; Trinsicon†; ***Turk.:*** Blood Builder; Epargriseovit; Ferplex Fol; Ferro-Vital; Ferrum Fort Hausmann; Folic Plus; Gyno-Tardyferon; Gynoferon; Maltofer Fol; Vi-Fer; ***UAE:*** Folicron; ***UK:*** Fefol; Ferrograd Folic; Galfer FA; Hematinic; Ironorm; Lexpec with Iron-M†; Lexpec with Iron†; Meterfolic; Pregaday; Slow-Fe Folic†; SoyPlus; ***USA:*** ABC to Z; Berocca Plus; Bevitamel; Centurion A–Z†; Certagen; Cevi-Fer†; Chromagen FA; Chromagen Forte; Compete; Contrin; Fe-Tinic Forte; Feocyte; Fero-Folic; Ferotrinsic; Ferralet Plus†; Ferrex Forte; Ferrex Forte Plus†; Ferrogels Forte; FOLTX; Formula B Plus; Geriot; Geritol Complete; Gevral T; Hematinic; Hematinic Plus; Hemocyte Plus; Hemocyte-F; Iberet-Folic†; Icar-C Plus; Ircon-FA†; Iromin-G; Livitrinsic-f; Nephro-Fer Rx†; Niferex Forte; Nu-Iron V; Parvlex; Poly-Iron Forte; PremesisRx; Pronemia Hematinic; Slow Fe with Folic Acid; Tandem F; Thera Hematinic; Theragenerix-H; Theravee Hematinic; TriHEMIC; Trinsicon; Vitafol; Yelets; Zodeac; ***Venez.:*** Calcibon Natal; Cobalfer; Fefol; Ferganic Folic; Ferro-Folic; Folifer B-12; Hepafol con B-12; Herrongyn; Intaferfol; Maltoferfol.

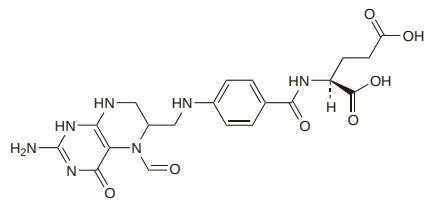
Folinic Acid *(BAN)*

Citrovorum Factor; Folínico, ácido; Leucovorin. 5-Formyltetrahydropteroylglutamic acid; *N*-[4-(2-Amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L(+)-glutamic acid.

Фолиновая Кислота

$C_{20}H_{23}N_7O_7$ = 473.4.

CAS — 58-05-9.



Calcium Folinate *(BANM, rINN)*

Calcii folinas; Calcii Folinas Hydricus; Calcium, folinate de; Calcium Folinate-SF; Calcium Leucovorin; Folinate de Calcium; Folinato cálcico; Kalcio folinatas; Kalciumfolinat; Kalcium-folinát; Kalcium-folinát hydrát; Kalsiumfolinaatti; Kalsiyum Folinat; Kalsiyum Lökovorin; Leucovorin Calcium; NSC-3590. The calcium salt of folinic acid (1:1).

Кальция Фолинат

$C_{20}H_{21}CaN_7O_7$ = 511.5.

CAS — 1492-18-8 (anhydrous calcium folinate); 41927-89-3 (calcium folinate pentahydrate); 6035-45-6 (calcium folinate pentahydrate).

ATC — V03AF03.

ATC Vet — QV03AF03.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*. *Chin.* includes the pentahydrate ($C_{20}H_{21}CaN_7O_7,5H_2O$ = 601.6).

Ph. Eur. 6.2 (Calcium Folinate). A white or light yellow, amorphous or crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in acetone. A 2.5% solution in water has a pH of 6.8 to 8.0. Store in airtight containers. Protect from light.

USP 31 (Leucovorin Calcium). A yellowish-white or yellow, odourless, powder. Very soluble in water; practically insoluble in alcohol. Protect from light.

Incompatibility. Calcium folinate and fluorouracil, with or without 5% glucose, were incompatible when mixed in various ratios and stored in PVC containers at various temperatures.[1]

1. Trissel LA, *et al*. Incompatibility of fluorouracil with leucovorin calcium or levoleucovorin calcium. *Am J Health-Syst Pharm* 1995; **52:** 710–15.

Calcium Levofolinate *(BAN, rINN)*

Calcii Levofolinas; Calcii levofolinas pentahydricus; Kalcio levofolinatas; Kalciumlevofolinat; Kalcium-levofolinát pentahydrát; Kalcium-levofolinát-pentahidrát; Kalciumlevofolinatpentahydrat; Kalsiumlevofolinaatti; Kalsiumlevofolinaattipentahydraatti; Levofolinate; Lévofolinate calcique pentahydraté; Lévofolinate de Calcium; Levofolinato de calcio; Levoleucovorin Calcium *(USAN)*. The calcium salt of the isomer of *S*-folinic acid (1:1).

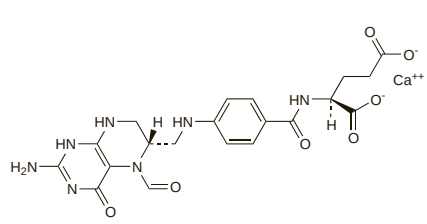
Кальция Левофолинат

$C_{20}H_{21}CaN_7O_7,5H_2O$ = 601.6.

CAS — 80433-71-2 (anhydrous calcium levofolinate).

ATC — V03AF04.

ATC Vet — QV03AF04.



(anhydrous calcium levofolinate)