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

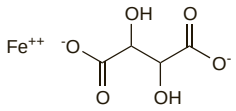
Ferrosi Tartras; Ferroso, tartrato.

$C_4H_4FeO_6,2H_2O$ = 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.

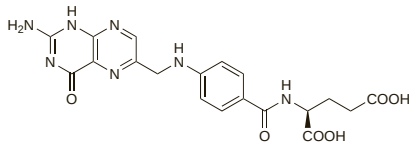
Фолиевая Кислота

$C_{19}H_{19}N_7O_6$ = 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-