

100 mg given four times daily by mouth significantly improved neuropathic pain in patients with diabetic polyneuropathy (see p.6).²

1. Thornalley PJ, et al. High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. *Diabetologia* 2007; **50**: 2164–70.
2. Haupt E, et al. Benfotiamine in the treatment of diabetic polyneuropathy—a three-week randomized, controlled pilot study (BEDIP Study). *Int J Clin Pharmacol Ther* 2005; **43**: 71–7.

Wernicke-Korsakoff syndrome. The Wernicke-Korsakoff syndrome is a manifestation of thiamine deficiency seen particularly in alcoholics, but which may accompany other conditions including starvation or prolonged fasting, or persistent vomiting. It was originally classified as two separate disorders, Wernicke's encephalopathy and Korsakoff's syndrome, but these are now thought to represent aspects of a single pathological process.^{1,2}

Classical Wernicke's symptoms comprise confusion, ataxia, ophthalmoplegia, and nystagmus. Ophthalmoplegia and ataxia may precede the mental symptoms by some days. Hypothermia may be seen, and collapse and sudden death may occur in some patients. The manifestations of Korsakoff's syndrome are short-term memory loss, learning deficits, and confabulation. The conditions are associated with demyelination and glial proliferation, as well as haemorrhagic lesions, mainly in the periventricular regions of the brain; characteristic biochemical abnormalities include raised serum-pyruvate concentration, which has been postulated as a cause of encephalopathy.³

Early recognition and treatment is important, both because of the risk of collapse and sudden death,⁴ and to prevent irreversible damage to the CNS. Korsakoff symptoms respond less well to treatment than those associated with Wernicke's encephalopathy,⁵ and may indeed only become evident on treatment.

Treatment is with parenteral thiamine, preferably intravenously, to ensure adequate absorption; any risks of parenteral treatment are considered justifiable.^{1,2,6,7} Although as little as 2 or 3 mg may be enough to reverse the ocular symptoms, which generally begin to improve in 1 to 6 hours, doses of at least 100 mg should be given initially. (In practice a typical dose is 500 mg given intravenously with other vitamins every 8 hours, for 2 days if symptoms persist, and followed by 100 mg twice daily orally, or 250 mg daily intravenously until the patient can take oral thiamine.^{6,8}) The ataxia and acute confusional state may also resolve dramatically although improvement may not be noted for days or months. Even several months after the onset of symptoms, treatment with high doses of thiamine has occasionally resulted in recovery.⁹ The effects of the syndrome on memory are much harder to reverse. Some 25% of patients make a full, and 50% a partial, recovery.⁵

1. Cook CCH, et al. B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. *Alcohol Alcohol* 1998; **33**: 317–36.
2. Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol* 2000; **35** (suppl): 2–7.
3. Petrie WM, Ban TA. Vitamins in psychiatry: do they have a role? *Drugs* 1985; **30**: 58–65.
4. Reuler JB, et al. Wernicke's encephalopathy. *N Engl J Med* 1985; **312**: 1035–9.
5. Anonymous. Korsakoff's syndrome. *Lancet* 1990; **336**: 912–13.
6. Cook CCH, Thomson AD. B-complex vitamins in the prophylaxis and treatment of Wernicke-Korsakoff syndrome. *Br J Hosp Med* 1997; **57**: 461–5.
7. Cook CCH. Prevention and treatment of Wernicke-Korsakoff syndrome. *Alcohol Alcohol* 2000; **35** (suppl): 19–20.
8. Chataway J, Hardman E. Thiamine doses for alcohol withdrawal. *Br J Hosp Med* 1994; **51**: 615.
9. Carota A, Schneider A. Dramatic recovery from prolonged Wernicke-Korsakoff disease. *Eur Neurol* 2005; **53**: 45–6.

Preparations

BP 2008: Thiamine Injection; Thiamine Tablets; Vitamins B and C Injection; **BPC 1973:** Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;

USP 31: Thiamine Hydrochloride Elixir; Thiamine Hydrochloride Injection; Thiamine Hydrochloride Tablets; Thiamine Mononitrate Elixir

Proprietary Preparations (details are given in Part 3)

Arg: Megastene; **Austral:** Beta-Sol†; **Betamin:** **Austria:** Beneuran; Bevitol; Dido-B; **Belg:** Beneura; Beneuro; **Betamine:** **Braz:** Arcalion; **Beneva:** Benum; **Neumvit;** **Canad:** Betaxin†; **Chile:** Arcalion; **Betamin†;** **Cz:** Benfogamma; **Thiabene;** **Fin:** Neuramin; **Vita-B1;** **Fr:** Arcalion; **Beneva;** **Bevitine;** **Ger:** Aneurin†; **B1-ASmedic;** **B Vicotraf†;** **Betabin;** **Milgamma** mono; **Gr:** Arcalion; **Beneva;** **Hong Kong:** Arcalion; **Super B1;** **Hung:** Benfogamma; **Beres B1;** **India:** Arcalion; **Benalgin;** **Indon:** Alinamin; **Arcalion;** **Beston;** **Licobevit;** **Ir:** Beneva†; **Ital:** Beneva; **Bivitas†;** **Jpn:** Alinamin-F; **Neuvita;** **Malaysia:** Arcalion; **Mex:** Benal; **Beneva;** **Carzilas;** **Fortical;** **MTX-2 Alf;** **TTC†;** **X-2;** **Philipp:** Arcalion; **Drexabion;** **Hybutin;** **Jaga;** **Lixtriss;** **Meganerv;** **Nervafin;** **Nervilin;** **Neuro-Bis;** **Neurobox†;** **Neurobion;** **Neurolin†;** **Polynerv;** **Supraneuron;** **Vineuron;** **Pol:** Alinamin; **Port:** Arcalion; **Trifosfaneurina;** **Vitanidia;** **Rus:** Benfogamma (Бенфогамма); **Enerion** (Энерион); **Singapore:** Arcalion; **Spain:** Arcalion; **Beneva;** **Neurostop;** **Summenal†;** **Swed:** Beneva; **Betabion;** **Switz:** Arcalion; **Beneva;** **Nicobrevin** N†; **Thal:** Alinamin-F; **Arcalion;** **Menamin†;** **Turk:** Arcalion; **Bevigon;** **UAE:** Thiavit; **UK:** Beneva; **Tyvera;** **Venez:** Arcalion; **Beplus;**

Multi-ingredient: **Arg:** Algio Nervomax; Algio Nervomax Fuerte; Co-Tioctan; **Cobenexol** Forte; **Cobenexol** Fuerte; **CVP B1 B6 B12†;** **Dexabion;** **Dolo Nervobion;** **Dolo Nervobion** 10000; **Dorixan B1 B6 B12†;** **Dr Calm†;** **Klosidol B1 B6 B12†;** **Nervobion** Fuerte; **Nervomax** TB12; **Valeriana** Diates; **Venostasin;** **Austral:** Berberis Complex; **Austria:** Ambene N; **Arca-Be;** **Beneuran** compositum; **Beneuran** Vit B-Komplex†; **Calcisian B + C;** **Diclovit;** **Dilaescol;** **Dolo-Neurobion;** **Neurobion;** **Neuromerck;** **Neuromultivit;** **Pronerv;** **Belg:** **Betapyr;** **Neurobion;** **Vioneurin†;** **Braz:** **Aminocid†;** **Bicavine;** **Cianotrat-Dexa;** **Citoneurin;** **Dexa-Citoneurin;** **Dexa-Cronobe;** **Dexa-Neuriber†;** **Dexacodal;** **Dexador;** **Dexadoze;** **Dexagil;** **Dexaneurin;** **Dex-**

aneval†; **Doxal;** **Dzouenerin;** **Espasmocron;** **Fol Sang;** **Lisan†;** **Sulfato** Ferroso Composto; **Sulfozof†;** **Trinrubin†;** **Venofort†;** **Venostasin†;** **Vitanerone†;** **Vitatonus;** **Canad:** **Penta-3B;** **Penta-3B + C;** **Penta-Thion†;** **Chile:** **Betovin†;** **Dolotol** 12; **Nefersil B;** **Neurobion†;** **Neurocam;** **Tol** 12; **Tol** 12 Plus; **Cz:** **Milgamma;** **Milgamma N;** **Neuromultivit;** **Fin:** **Neurobion;** **Neurovitan†;** **Fr:** **Hexagocin;** **Vitathion;** **Ger:** **B-Komplex** forte; **Bevit** Forte; **Dolo-Neurobion** forte†; **Dolo-Neurobion** N†; **Hewedolol** neuro; **Medivitan N** Neuro; **Milgamma;** **Milgamma N;** **Milgamma-NA;** **Millineuron** NA; **Neuralysan** S†; **Neuro;** **Neuro** uno; **Neuro-AS N†;** **Neuro-B** forte; **Neuro-Effektol B;** **Neuro-Lichtenstein** M†; **Neuro-Lichtenstein** N; **Neuro-ratiopharm** N; **Neuro-ratiopharm†;** **Neuro-Vibolox;** **Neurobion** N; **Neurotrat** S; **Novirell** B Duo; **Pantovigrin** N; **Pleomix-B;** **Regepith;** **Vitact†;** **Vitamin** B duo; **Gr:** **Neurobion;** **Hong Kong:** **3B;** **Alinamin-F;** **Childrens** **Coltalin** with Vit B; **Coltalin** with Vit B; **I:** **Magesto;** **Milgamma;** **Neuro** B1-6-12†; **Neurobion;** **Neuromin;** **Neurorubine;** **Nevramin;** **Princi-B** Fort; **Regepith†;** **Tonterin†;** **Vibion;** **Vida** **Neurotab;** **Vidaclofen-Plus;** **Hung:** **Milgamma;** **Milgamma N;** **Neurobion;** **India:** **Sioneuron;** **Vitneurin;** **Indon:** **Abajis;** **Arsinal;** **Betrium;** **Bictrion;** **Biocombin;** **Biomega;** **Biomex;** **Butamidon;** **Corobion;** **Corsaneuron;** **Daneuron;** **Dolo** **Scanneuron;** **Dolo-Licobion;** **Dolo-Neurobion;** **Dolofenac;** **Farbio;** **Foreanur†;** **Fundamin-E;** **Goralgin;** **Ikanuron;** **Ikanuron** S; **Lapibion;** **Licobion;** **Mersibion;** **Nervitone;** **Nervitone E;** **Neuralgin** RX; **Neuro** Panstop; **Neuro-Beston;** **Neurobat;** **Neurobat** A; **Neurobion;** **Neurobiovit;** **Neurodex;** **Neurogen;** **Neurohax;** **Neurophil;** **Neuropyramin;** **Neurosanbe;** **Neurosanbe** Plus; **Neurotrat;** **Neurotrop** Plus; **Neurovit** E; **Nevradin;** **Nevramin;** **Penagon;** **Ponconeuron;** **Primabion;** **Pritagesc;** **Scanneuron;** **Sohobion;** **Solaneuron;** **Stileran;** **Supranal;** **Tocobion;** **Trimate-E;** **Tropineuron;** **Israel:** **Calmanervin;** **Tribemim;** **Ital:** **Adenobeta†;** **Adenoplex;** **Adenovit†;** **Antiadiposo;** **Benexol** B12; **Dobetin** con **Vitamin** B1; **Dobetin** Totale; **Emazian** B12†; **Emoantitossina†;** **Empoon;** **Esaglut†;** **Fibronevina;** **Folepar** B12; **Fosforilas;** **Fosfouipi** **Vitaminico†;** **Mionevras;** **Neuraben;** **Neurofal†;** **Odontalgico** Dr Knapp con Vit B1; **Rubiovit;** **Trinevrina** B6; **Jpn:** **Neurovitan†;** **Malaysia:** **3B;** **Alinamin** B12†; **Flavettes** Neuroforte; **Fundamin-E;** **Neuro** B†; **Neurobion;** **Neurorubine;** **Neurovit†;** **Nevramin;** **Princi-B** Fort; **Re-B;** **Vitabion;** **Mex:** **Aniflam** Forte; **B1-12-15;** **Bedocil†;** **Benexol** B12; **Betrox;** **Cobotaxina;** **Dexabion;** **Diclo-vith-B;** **Dodemina** Tri; **Dolo-Neurobion;** **Dolo-Pangavit;** **Dolo-Tiaminal;** **Doxemina;** **Ducilion;** **Ferrotrop;** **Forvin;** **Innobion;** **Lipovitasi-Or;** **Macrox-5;** **Neuralin;** **Neurobion;** **Nuro-B;** **Odexan;** **Ofzim;** **Pangavit** B; **Pangavit** Hypak; **Pangavit** Pediatrico; **Revitaliv-C;** **Selectadoco;** **Suma-B;** **Tiabexol;** **Tiamidexal;** **Tiaminal** B; **Tiaminal** B Trivalente; **Tribedoco;** **Tribedoco** Composto; **Tribedox†;** **Trineurovita;** **Trineurovita** Composto; **Uni-Dox;** **Neth:** **Neurobion;** **Princi** B1 + B6; **Philipp:** **Dolo-Neurobion;** **Glutaphos;** **Hinuron-E;** **Meganerv** F-A; **Neuroforte-E;** **Nevramin;** **Nuron-E;** **Vitanerv;** **Pol:** **Milgamma** N; **Port:** **Cebrotex** Forte; **Linamin** Plus†; **Neurobion;** **Rus:** **Aescusan** (Эскузан); **Benalgin** (Бенальгин); **Milgamma** (Мильгамма); **Neuromultivit** (Нейромультивит); **S.Afr:** **Kiddie** Vite†; **Neurobion;** **Singapore:** **Alinamin** B12†; **Alinamin-F;** **Daneuron;** **Neurobion;** **Neurodex;** **Neuroforte;** **Neurorubine;** **Neurovit;** **Neuroxel;** **Nevramin;** **Princi-B** Fort; **Spain:** **Acetuber;** **Antineurina;** **Benexol** B1 B6 B12; **Bester** Complex; **Calmante** **Vitaminado** PG; **Calmante** **Vitaminado** PG Efervescente; **Calmante** **Vitaminado** Rinver; **Dalamon†;** **Hidroxil** B12 B6 B1; **Inzitan;** **Mederebro;** **Meloka;** **Menalgil** B6; **Nervobion;** **Neuromade;** **Neurostop** Complex; **Pazbronquial;** **Quimpedor;** **Refugin;** **Viadrest†;** **Swed:** **Neurobion;** **Switz:** **Benexol** B12; **Neurobion;** **Trilagvit;** **Thal:** **3B;** **Alinamin** B12†; **Alinamin-F;** **B-100** Complex; **Beromin;** **Cydoximine-B†;** **Cyriamine;** **Diagest;** **Digestin;** **Douzabox;** **Endogest†;** **Genavit;** **Hemolax;** **Mesto-Of;** **Neubee;** **Neurobox;** **Neurobion;** **Nevramin;** **Nuro-B;** **Nuvit;** **Princi-B;** **Re-B** Forte; **Tribesian;** **Trivit-B;** **Vita-B;** **Vitabion;** **Vitamedin†;** **Vitron;** **Turk:** **Benexol;** **Benol;** **Benoral;** **Bevitab;** **Bevitol;** **Nerox-B;** **Neurogisevit;** **Neurovit;** **Neuvitan;** **Tribeksol;** **UAE:** **3V;** **UK:** **Don't** Bug Me; **Labiton†;** **Quiet** **Lice;** **Venez:** **Bedoyecta;** **Beufosin;** **Briomet;** **Deca-Lentermina** Complex; **Dobetin** Composto; **Mega-Neubion;** **Miovit;** **Neubion;** **Neuribe;** **Rubinal;** **Rubrinex;** **Tres-Be.**

Used as an adjunct in: **Indon:** Nufadoxin.

Vitamin B₂ Substances

Vitamina B₂.

Riboflavin (BAN, rINN)

E101; Lactoflavin; Riboflavin†; Riboflavina; Riboflavinas; Riboflavine; Riboflavinum; Ryboflawina; Vitamin B₂; Vitamin G. 7.8. Dimethyl-10-(1'-o-riboityl)isalloxazine; 3,10-Dihydro-7,8-dimethyl-10-(D-ribo-2,3,4,5-tetrahydroxypentyl)benzopteridine-2,4-dione.

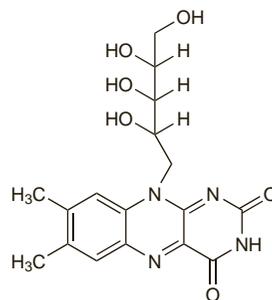
Рибофлавин

C₁₇H₂₀N₄O₆ = 376.4.

CAS — 83-88-5.

ATC — A11HA04.

ATC Vet — QAl1HA04.



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

Ph. Eur. 6.2 (Riboflavin). A yellow or orange-yellow crystalline powder. It exhibits polymorphism. Very slightly soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light. Solutions deteriorate on exposure to light, especially in the presence of alkali.

USP 31 (Riboflavin). A yellow to orange-yellow crystalline powder, having a slight odour. When dry, it is not appreciably affected by diffused light, but in solution light induces quite rapid deterioration, especially in the presence of alkalis. Very slightly soluble in water, in alcohol, and in isotonic sodium chloride solution; insoluble in chloroform and in ether; soluble in dilute solutions of alkalis. Its saturated solution in water is neutral to litmus. Store in airtight containers. Protect from light.

Riboflavin Sodium Phosphate (BANM, rINNM)

Fosfato sódico de riboflavina; Natrii Riboflavini Phosphas; Riboflaviniinatriumfosfaatti; Riboflavin fosfát sodná sůl; Riboflavin 5'-Phosphate Sodium; Riboflavine, phosphate sodique de; Riboflavine Phosphate (Sodium Salt); Riboflavine Sodium Phosphate; Riboflavin-foszfát-nátrium; Riboflavini natrii phosphas; Riboflavini-natriumfosfat; Riboflavino natrio fosfatas; Vitamin B₂ Phosphate. The sodium salt of riboflavin 5'-phosphate.

Натрия Рибофлавина Фосфат

C₁₇H₂₀N₄NaO₉P = 478.3.

CAS — 130-40-5.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Chin. and *US* specify the dihydrate salt.

Ph. Eur. 6.2 (Riboflavin Sodium Phosphate). A yellow or orange-yellow, hygroscopic, crystalline powder. Soluble in water; very slightly soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 31 (Riboflavin 5'-Phosphate Sodium). A fine, orange-yellow, hygroscopic, crystalline powder, having a slight odour. When dry, it is not affected by diffused light, but when in solution light induces rapid deterioration. Sparingly soluble in water. pH of a 1% solution in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Large doses of riboflavin result in a bright yellow discoloration of the urine that may interfere with certain laboratory tests.

Breast feeding. Supplementation significantly increased riboflavin concentration in the breast milk of women compared with those not given riboflavin. Significant differences between the two groups decreased over the period from 1 to 6 weeks postpartum; both groups of women had breast milk concentrations above previously reported normal values, and the authors concluded that supplementation was not necessary in healthy, well-nourished women.¹ The American Academy of Pediatrics considers the use of riboflavin to be usually compatible with breast feeding.²

1. Nail PA, et al. The effect of thiamin and riboflavin supplementation on the level of those vitamins in human breast milk and urine. *Am J Clin Nutr* 1980; **33**: 198–204.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 09/01/06)

Pharmacokinetics

Riboflavin is readily absorbed from the gastrointestinal tract. Although riboflavin is widely distributed to body tissues little is stored in the body.

Riboflavin is converted in the body to the coenzyme flavine mononucleotide (FMN); riboflavin 5'-phosphate) and then to another coenzyme flavine adenine dinucleotide (FAD). About 60% of FMN and FAD are bound to plasma proteins. Riboflavin is excreted in urine, partly as metabolites. As the dose increases, larger amounts are excreted unchanged. Riboflavin crosses the placenta and is distributed into breast milk.

Human Requirements

The riboflavin requirement is often related to the energy intake but it appears to be more closely related to resting metabolic requirements. A daily dietary intake of about 1.1 to 1.8 mg of riboflavin is recommended. Liver, kidney, fish, eggs, milk, cheese, yeast, and some green vegetables such as broccoli and spinach are the richest sources of riboflavin. In general, little loss of riboflavin occurs during cooking, but considerable losses may occur if foods, especially milk, are exposed to sunlight.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) have been published for riboflavin¹ and similarly in the USA recommended dietary allowances (RDAs) have been set.² Differing amounts are recommended for infants and children of varying ages, for adult males and females of varying ages, and for pregnant and lactating women; the differences between age groups are intended to reflect the changes in caloric intakes at these ages. In the UK the

reference nutrient intake (RNI) is 1.3 mg daily and 1.1 mg daily for adult males and females respectively; the estimated average requirement (EAR) is 1.0 mg daily and 0.9 mg daily respectively. In the USA the RDAs for adult males and females are 1.3 and 1.1 mg daily respectively.

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 B₆, folate, vitamin B₁₂, 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

Riboflavin, a water-soluble vitamin, is essential for the utilisation of energy from food. The active, phosphorylated forms, flavine mononucleotide (FMN) and flavine adenine dinucleotide (FAD), are involved as coenzymes in oxidative/reductive metabolic reactions. Riboflavin is also necessary for the functioning of pyridoxine and nicotinic acid.

Riboflavin deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a well-defined syndrome known as ariboflavinosis, characterised by cheilosis, angular stomatitis, glossitis, keratitis, surface lesions of the genitalia, and seborrhoeic dermatitis. There may also be normocytic anaemia and ocular symptoms including itching and burning of the eyes, and corneal vascularisation. Some of these symptoms may, in fact, be due to other vitamins such as pyridoxine or nicotinic acid which do not function correctly in the absence of riboflavin. Riboflavin deficiency may also occur with other vitamin B-complex deficiency states such as pellagra.

Riboflavin is used in the treatment and prevention of riboflavin deficiency. It is usually given in oral doses of 1 or 2 mg for prophylaxis; up to 30 mg daily in divided doses is used for treatment. Riboflavin, as the sodium phosphate, is also a component of intramuscular or intravenous vitamins B and C injections; riboflavin sodium phosphate 1.27 g is equivalent to about 1 g of riboflavin.

Riboflavin tetrabutryate has also been used.

Riboflavin is also used as a colouring agent for food.

Glutaric aciduria. Milder forms of glutaric aciduria type II (p.1451) may respond to riboflavin.¹ Treatment with riboflavin 50 mg daily resulted in progressive improvement in a 4-year-old boy, with full recovery after 1 year. His brother, who had sustained permanent brain damage after epileptic seizures, showed moderate clinical improvement with riboflavin therapy.² In an adult patient with a history of recurrent pancreatitis and exercise intolerance, treatment with riboflavin 120 mg daily and levocarnitine resulted in no further episodes, although abnormal concentrations of amino acids were still apparent in her urine.³

1. Gregersen N, et al. Riboflavin responsive glutaric aciduria type II. *Prog Clin Biol Res* 1990; **321**: 477-94.
2. Uziel G, et al. Riboflavin-responsive glutaric aciduria type II presenting as a leukodystrophy. *Pediatr Neurol* 1995; **13**: 333-5.
3. Liang W-C, et al. Riboflavin-responsive glutaric aciduria type II with recurrent pancreatitis. *Pediatr Neurol* 2004; **31**: 218-21.

Migraine. Results from open studies^{1,2} and a placebo-controlled trial³ have suggested that riboflavin in high doses (400 mg daily) might be of some benefit in the prophylaxis of migraine attacks (p.616).

1. Schoenen J, et al. High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. *Cephalalgia* 1994; **14**: 328-9.
2. Boenke C, et al. High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. *Eur J Neurol* 2004; **11**: 475-7.
3. Schoenen J, et al. Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial. *Neurology* 1998; **50**: 466-70.

Preparations

BP 2008: Vitamins B and C Injection;
BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;
USP 31: Riboflavin Injection; Riboflavin Tablets.

Proprietary Preparations (details are given in Part 3)

Belg: Berivine; Ribon; **Fin:** Vita-B2; **Fr:** Belfavine; **Ger:** B2-ASmedic; **Hong Kong:** FAD Ophthalmic Soln; Hilon; **Indon:** Alinamin; **Thai:** Boflavin.

Multi-ingredient: **Austral:** Antioxidant Forte Tablets; Antioxidant Tablets; Extralife Eye-Care; Liv-Detox†; **Austria:** Beneruan Vit B-Komplex†; **Braz:** Sulfatofer†; **Ger:** Kwim†; **Hong Kong:** Alinamin-F; **India:** Hepamerz; **Indon:** Matase; **Ital:** Emazian B12†; Emoantitossina†; Facovit; Fos-

forilis; Neurofal†; **Jpn:** Neurovitant†; **Mex:** Pangavit Pediatrica; **Philipp:** Godex; **Pol:** Biovision; **Singapore:** Alinamin-F; **Spain:** Aftasone B₆ C; **Thai:** Alinamin-F; B-100 Complex; **Turk:** Neurovit; **UK:** Quiet Life; Se-Power; **USA:** Cerefolin.

Vitamin B₆ Substances

Vitamina B₆.

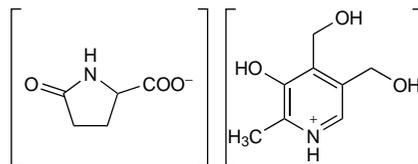
Vitamin B₆ is usually available as pyridoxine but the term is also used to refer to the related compounds, pyridoxal and pyridoxamine.

Metadoxine

Metadoxina; Pyridoxine Pidolate. Pyridoxine 1-5-oxopyrrolidine-2-carboxylate.

$C_8H_{11}NO_3$, $C_5H_7NO_3 = 298.3$.

CAS — 74536-44-0.



Pyridoxal Phosphate

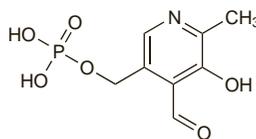
Codecarboxylase; MC-I; Piridoxal, fosfato de; Pyridoxal 5-Phosphate. 3-Hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde 5'-phosphate.

$C_8H_{10}NO_6P = 247.1$.

CAS — 54-47-7.

ATC — A11HA06.

ATC Vet — QA11HA06.

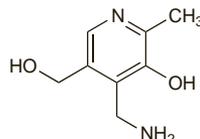


Pyridoxamine Hydrochloride

Piridoxamina, hidrokloruro de; Pyridoxamine Dihydrochloride. 4-Aminomethyl-5-hydroxy-6-methyl-3-pyridinemethanol hydrochloride.

$C_8H_{12}N_2O_2 \cdot 2HCl = 241.1$.

CAS — 524-36-7.



(pyridoxamine)

Pyridoxine Hydrochloride (BANM, rINNM)

Adermine Hydrochloride; Hidrokloruro de piridoxina; Piridoksin Hidroklorid; Piridoksin hidrokloridas; Piridossina Cloridrato; Pindoxin-hidroklorid; Pirydoksyn chlorowodorek; Pyridoksiini-hidroklorid; Pyridoxine, chlorhydrate de; Pyridoxin-hydrochlorid; Pyridoxinhydroklorid; Pyridoxini hydrochloridum; Pyridoxinii Chloridum; Pyridoxinium Chloride; Pyridoxol Hydrochloride; Vitamin B₆, 3-Hydroxy-4,5-bis(hydroxymethyl)-2-picoline hydrochloride.

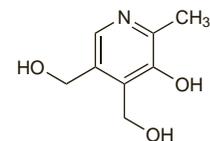
Пиридоксина Гидрохлорид

$C_8H_{11}NO_3 \cdot HCl = 205.6$.

CAS — 65-23-6 (pyridoxine); 58-56-0 (pyridoxine hydrochloride).

ATC — A11HA02.

ATC Vet — QA11HA02.



(pyridoxine)

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

Ph. Eur. 6.2 (Pyridoxine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 2.4 to 3.0. Protect from light.

USP 31 (Pyridoxine Hydrochloride). White or practically white crystals or crystalline powder. Soluble 1 in 5 of water and 1 in 115 of alcohol; insoluble in ether. Its solutions in water have a pH of about 3. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Long-term use of large doses of pyridoxine is associated with the development of severe peripheral neuropathies; the dose at which these occur is controversial (see below).

Breast feeding. Vitamin B₆ is excreted into breast milk.^{1,2} While some have expressed concern over the inhibition of breast milk secretion by pyridoxine,³ others have cautioned that pyridoxine deficiency may cause seizures in the neonate.⁴ The American Academy of Pediatrics considers the use of pyridoxine to be usually compatible with breast feeding.⁵

1. West KD, Kirksey A. Influence of vitamin B₆ intake on the content of the vitamin in human milk. *Am J Clin Nutr* 1976; **29**: 961-9.
2. Roepke JLB, Kirksey A. Vitamin B₆ nutrition during pregnancy and lactation: I. Vitamin B₆ intake, levels of the vitamin in biological fluids, and condition of the infant at birth. *Am J Clin Nutr* 1979; **32**: 2249-56.
3. Greentree LB. Dangers of vitamin B₆ in nursing mothers. *N Engl J Med* 1979; **300**: 141-2.
4. Lande NI. More on dangers of vitamin B₆ in nursing mothers. *N Engl J Med* 1979; **300**: 926-7.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776-89. Correction. *ibid.*: 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 09/01/06)

Effects on the nervous system. Severe sensory neuropathy has been described in patients receiving large doses of pyridoxine (2 to 6 g daily) for periods of 2 to 40 months.¹ There has, however, been debate as to whether smaller doses can produce such effects. Some contend that amounts of pyridoxine below this level are unlikely to produce toxic effects.^{2,3} However, there have been some case reports^{4,5} with amounts up to about 500 mg daily and prolonged use of even lower doses (about 200 mg daily or less) may also cause sensory peripheral neuropathy.⁶ After a review of the possible toxicity associated with lower doses of pyridoxine, proposals were put forward in the UK to limit the dose freely available in dietary supplements to 10 mg daily; products supplying up to 50 mg daily would continue to be available from pharmacies and higher doses would only be available on prescription.⁷ These proposals were heavily contested.^{7,8} An upper limit of 100 mg daily has been suggested in the USA.⁸

1. Schaumburg H, et al. Sensory neuropathy from pyridoxine abuse: a new megavitamin syndrome. *N Engl J Med* 1983; **309**: 445-8.
2. Pauling L. Sensory neuropathy from pyridoxine abuse. *N Engl J Med* 1984; **310**: 197.
3. Baker H, Frank O. Sensory neuropathy from pyridoxine abuse. *N Engl J Med* 1984; **310**: 197.
4. Berger A, Schaumburg HH. More on neuropathy from pyridoxine abuse. *N Engl J Med* 1984; **311**: 986.
5. Waterston JA, Gilligan BS. Pyridoxine neuropathy. *Med J Aust* 1987; **146**: 640-2.
6. Dordain G, Deffond D. Neuropathies à la pyridoxine: revue de la littérature. *Therapie* 1994; **49**: 333-7.
7. Collier J. Vitamin B-6: food or medicine? *BMJ* 1998; **317**: 92-3.
8. Anonymous. Still time for rational debate about vitamin B₆. *Lancet* 1998; **351**: 1523.

Interactions

Pyridoxine reduces the effects of levodopa (see p.808), but this does not occur if a dopa decarboxylase inhibitor is also given. Pyridoxine reduces the activity of al-tretamine. It has also been reported to decrease serum concentrations of phenobarbital (p.494) and phenytoin (p.500). Many drugs may increase the requirements for pyridoxine; such drugs include hydralazine, isoniazid, penicillamine, and oral contraceptives.

Pharmacokinetics

Pyridoxine, pyridoxal, and pyridoxamine are readily absorbed from the gastrointestinal tract after oral doses