

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

1. Thormalley 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.<sup>1,2</sup>

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.<sup>3</sup>

Early recognition and treatment is important, both because of the risk of collapse and sudden death,<sup>4</sup> and to prevent irreversible damage to the CNS. Korsakoff symptoms respond less well to treatment than those associated with Wernicke's encephalopathy,<sup>5</sup> 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.<sup>1,2,6,7</sup> 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.<sup>6,8</sup>) 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.<sup>9</sup> The effects of the syndrome on memory are much harder to reverse. Some 25% of patients make a full, and 50% a partial, recovery.<sup>5</sup>

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:** Beneran; Bevitol; Dido-B; **Belg:** Benerva; Benerol; Betamine; **Braz:** Arcalion; Benerva; Benelum; Neuvit; **Canad:** Betaxin†; **Chile:** Arcalion; Betamin†; **Cz:** Benfogamma; Thiabene; **Fin:** Neuramin; Vita-B1; **Fr:** Arcalion; Benerva; Bevitine; **Ger:** Aneurin†; B1-ASmedix; B. Vicotraf†; Betabion; Milgamma mono; **Gr:** Arcalion; Benerva; **Hong Kong:** Arcalion; Super B1; **Hung:** Benfogamma; Beres B1; **India:** Arcalion; Benalgis; **Indon:** Alinamin; Arcalion; Beston; Licobevit; **Irl:** Benerva†; **Ital:** Benerva; Bivitas†; **Jpn:** Alinamin-F; Neuvita; **Malaysia:** Arcalion; **Mex:** Benal; Benerva; Carzilas; Fortical; MTX-2 Alf; TTC†; X-2; **Philipp:** Arcalion; Drexalion; Hybutin; Jaga; Lixtrax; Megener; Nervafix; Nervalin; Neuro-Bs; Neurobexol; Neurobion; Neurolink; Polynerv; Supraneuron; Vineuron; **Pol:** Benfogamma; **Port:** Arcalion; Trifosfaneurina; Vitandina; **Rus:** Benfogamma (Бенфогамма); Enerion (Энерион); **Singapore:** Arcalion; **Spain:** Arcalion; Benerva; Neurostop; Summenal†; **Swed:** Benerva; Betabion; **Switz:** Arcalion; Benerva; Nicobrevin N†; **Thal:** Alinamin-F; Arcalion; Menamin†; **Turk:** Arcalion; Bevigir; **UAE:** Thiavit; **UK:** Benerva; Tyvera; **Venez:** Arcalion; Beplus.

**Multi-ingredient:** **Arg:** Algio Nervomax; Algio Nervomax Forte; Co-Tioctan; Cobenexol Forte; Cobenexol Forte; CVP B1 B6 B12†; Dexabion; Dolo Nervobion; Dolo Nervobion 10000; Dolorixina B1 B6 B12; Dr Calm†; Kiosidol B1 B6 B12; Nervobion Forte; Nervobion TBI2; Valeriana Diates; Venostasin; **Austral:** Berberis Complex; **Austria:** Ambene N; Arca-Ba; Beneran compositum; Beneran Vit B-Komplex†; Calisan B + C; Didlovit; Dilaescol; Dolo-Neurobion; Neurobion; Neuromerck; Neuromultivit; Pronerv; **Belg:** Betapyr; Neurobion; Vioneurin†; **Braz:** Aminoacid†; Bicavine; Cianoatrat-Dexa; Citoneurin; Dexa-Citoneurin; Dexa-Cronobex; Dexa-Neuribet†; Dexacabal; Dexador; Dexadoze; Dexagil; Dexaneurin; Dex-

aneval†; Doxal; Dozeneurin; Espasmocron; Fol Sang; Lisant†; Sulfato Feroso Composito; Sulfatofer†; Trirubin†; Venofort†; Venostasin†; Vitaneuron†; Vitaminus; **Canad:** Penta-3B; Penta-3B + C; Penta-Thion†; **Chile:** Betonvit†; Dolotol 12; Nefersil B; Neurobion†; Neurocam; Tol 12; Tol 12 Plus; **Cz:** Milgamma; Milgamma N; Neuromultivit; **Fin:** Neurobion; Neurovit†; **Fr:** Hexaqueine; Vitathion; **Ger:** B-Komplex forte; Bevit Forte; Dolo-Neurobion forte†; Dolo-Neurobion N†; Hwexodol neuro; Medivita N Neuro; Milgamma; Milgamma N; Milgamma-NA; Milneuron NA; Neuralysan S†; Neuro; Neuro uno; Neuro-AS N†; neuro-B forte; Neuro-Effektin B; Neuro-Lichtenstein N; Neuro-Lichtenstein N; Neuro-ratiopharm N; Neuro-ratiopharm†; Neuro-Vibolex; Neurobion N; Neurotrat S; Novirell B Duo; Pantovigar N; Pleomix-B; Regepithel; Vitaject†; Vitamin B duo; **Gr:** Neurobion; **Hong Kong:** 3B; Alinamin-F; Childrens Coltalin with Vit B†; Coltalin with Vit B†; Magesto; Milgamma; Neuro B1-6-12†; Neurobion; Neuromin; Neurorubine; Nevramin; Princi-B Forte; Regepithel†; Tenterin†; Vibion; Vida Neurotab; Vidaclofen-Plus; **Hung:** Milgamma; Milgamma N; Neurobion; **India:** Sioneuron; Vitneurin; **Indon:** Abajis; Arsnal; Betriol; Bictron; Biocombin; Biomega; Biomex; Butamidol; Corobion; Corsaneuron; Daneuron; Dolo Scanneuron; Dolo-Licobion; Dolo-Neurobion; Dolofenac; Farbion; Foraneural; Fundamin-E; Goralgin; Ikaneuron; Ikaneuron Plus; Lipabion; 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; Neurotropis Plus; Neurovit E; Nevradin; Nevramin; Penagon; Ponconeuron; Primabion; Prtagase; Scanneuron; Sohobion; Solaneuron; Stileran; Supranal; Tocobion; Trimate-E; Tropineuron; **Israel:** Calmanervin; Tribemir; **Ital:** Adenobex†; Adenoplex; Adenovit†; Antiadiposo; Benexol B12; Dobetin con Vitamin B1; Dobetin Totale; Emazian B12†; Emonitossina†; Emopon; Esaglut†; Fibroneurina; Folepar B12; Fosforilas; Fosfotupit Vitaminico†; Mionevras†; Neurben; Neurofal†; Odontalgico Dr Knapp con Vit B1; Rubjovit; Trinevina B6; **Jpn:** Neurovit†; **Malaysia:** 3B; Alinamin B12†; Flavettes Neuroforte; Fundamin-E; Neuro B†; Neurobion; Neurorubine; Neurovit†; Nevramin; Princi-B Forte; Re-B; Vitabion; **Mex:** Aniflam Forte; B1-12-15; Bedocil†; Benexol B12; Beterox; Cobotaxina; Dexabion; Diclodiv-B; Dodemina Tri; Dolo-Neurobion; Dolo-Pangavit; Dolo-Tiaminal; Dowermina; Ducilol; Ferrotrop; Forvin; Innobion; Lipovitasi-Or; Macrox-5; Neuralin; Neurobion; Nuro-B; Odexan; Ofizim; Pangavit B; Pangavit Hypak; Pangavit Pediatrico; Revitalis-C; Selectadoc; Suma-B; Tiabexol; Tiamidexal; Tiaminal B†; Tiaminal B Trivalente; Tribedoce; Tribedoce Compuesto; Tribedoxyl†; Trineurovita; Trineurovita Compuesto; Uni-Dox; **Neth:** Neurobion; Princi B1 + B6; **Philipp:** Dolo-Neurobion; Glutaphos; Hiron-E; Meganerv F-A; Neuroforte-E; Nevramin; Nuron-E; Vitaneur; **Pol:** Milgamma N; **Port:** Cebrotex Forte; Linamin Plus†; Neurobion; **Rus:** Aescusan (Эскузан); Benalgis (Бенальгис); Milgamma (Мильгамма); Neuromultivit (Нейромультивит); **S.Afr:** Kiddie Vit†; Neurobion; **Singapore:** Alinamin B12†; Alinamin-F; Neurovit; Neurodex; Neurodex; Neuroforte; Neurobion; Neurovit; Neuroxol; Nevramin; Princi-B Forte; **Spain:** Acetuber; Antineurina; Benexol B1 B6 B12; Bester Complex; Calmante Vitaminado PG; Calmante Vitaminado PG Efervescente; Calmante Vitaminado Rinver; Dalamon†; Hidroxil B12 B6 B1; Izitain; Mederebro; Meloka; Menalgi B6; Nervobion; Neuromade; Neurostop Complex; Pazbronquial; Quimpeador; Refulgin; Viadestres†; **Swed:** Neurobion; **Switz:** Benexol B12; Neurorubin; Trilavag†; **Thal:** 3B; Alinamin B12†; Alinamin-F; B-100 Complex; Beromin; Cydoximine-B†; Cyrimamine; Digest; Digestin; Douzabox; Endogest†; Genavit; Hemolax; Mesto-Of; Neubex; Neurodex; Neurobion; Nevramin; Nuro-B; Nuvit; Princi-B; Re-B Forte; Tribesian; Trivit-B; Vita-B; Vitabion; Vitamedin†; Vitron; **Turk:** Benexol; Benel; Benoral; Bevitab; Bevitol; Nerox-B; Neurogrisevit; Neurovit; Neuvitan; Tribeksol; **UAE:** 3V; **UK:** Don't Bug Me; Labiton†; Quiet Life; **Venez:** Bedoyecta; Befosfin; Briomet; Deca-Lentemina Complex; Dobetin Compuesto; Mega-Neubion; Miovit; Neubion; Neuribe; Rubinal†; Rubinex; Tres-Be.

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

## Vitamin B<sub>2</sub> Substances

Vitamina B<sub>2</sub>.

**Riboflavin** (BAN, rINN)

E101; Lactoflavin; Riboflavin†; Riboflavina; Riboflavinas; Riboflavine; Riboflavinum; Ryboflawina; Vitamin B<sub>2</sub>; Vitamin G. 7.8-Dimethyl-10-(1'-o-ribityl)isalloxazine; 3,10-Dihydro-7,8-dimethyl-10-(p-ribo-2,3,4,5-tetrahydroxypentyl)benzopteridine-2,4-dione.

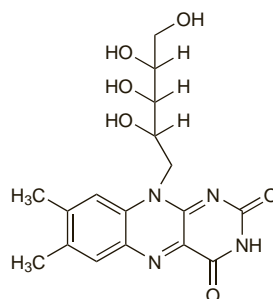
Рибофлавин

C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub> = 376.4.

CAS — 83-88-5.

ATC — A11HA04.

ATC Vet — QA11HA04.



**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, rINN)

Fosfato sódico de riboflavina; Natrii Riboflavini Phosphas; Riboflavininatriumfosfaat†; Riboflavin fosfat sodná sůl; Riboflavin 5'-Phosphate Sodium; Riboflavine, phosphate sodique de; Riboflavine Phosphate (Sodium Salt); Riboflavine Sodium Phosphate; Riboflavin-foszfát-nátrium; Riboflavini natrii phosphas; Riboflavin-natriumfosfat; Riboflavino natrio fosfatas; Vitamin B<sub>2</sub> Phosphate. The sodium salt of riboflavin 5'-phosphate.

Натрия Рибофлавина Фосфат

C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>NaO<sub>9</sub>P = 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.<sup>1</sup> The American Academy of Pediatrics considers the use of riboflavin to be usually compatible with breast feeding.<sup>2</sup>

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 riboflavin<sup>1</sup> and similarly in the USA recommended dietary allowances (RDAs) have been set.<sup>2</sup> 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