py in 192 infants with infantile spasms who were followed up for an average of 7.6 months,[8] there was complete cessation of spasms in 131 patients, a decrease in cluster frequency in 37, and no improvement in 24 (including deterioration in 1 infant). A crossover study comparing vigabatrin with corticotropin in 42 infants found that both drugs produced some benefit;[9] a larger multicentre comparison of treatment with prednisolone and tetracosactide versus vigabatrin found that the former produced better initial control, but that the treatments were equivalent after more prolonged follow-up to 12 to 14 months of age.[10] A review of the literature suggested that vigabatrin was particularly effective in infantile spasms associated with tuberous sclerosis;[11] the authors considered that its efficacy might be less in other forms of infantile spasm.[11] A later guideline[12] also tentatively concluded that vigabatrin was effective in the short-term treatment of infantile spasms including those associated with tuberous sclerosis.

1. French JA. Vigabatrin. *Epilepsia* 1999; **40** (suppl 5): S11–S16.
2. Gidal BE, *et al.* Vigabatrin: a novel therapy for seizure disorders. *Ann Pharmacother* 1999; **33:** 1277–86.
3. Lewis H, Wallace SJ. Vigabatrin. *Dev Med Child Neurol* 2001 **43:** 833–5.
4. Dalla Bernadina B, *et al.* Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. *Epilepsia* 1995; **36:** 687–91.
5. French JA, *et al.* A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. *Neurology* 1996; **46:** 54–61.
6. Malmgren K, *et al.* Cost analysis of epilepsy surgery and of vigabatrin treatment in patients with refractory partial epilepsy. *Epilepsy Res* 1996; **25:** 199–207.
7. Walker MC, *et al.* Long term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome. *BMJ* 1996; **313:** 1184–5.
8. Aicardi J, *et al.* Sabril IS Investigator and Peer Review Groups. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. *Epilepsia* 1996; **37:** 638–42.
9. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. *Epilepsia* 1997; **38:** 1270–4.
10. Lux AL, *et al.* The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *Lancet Neurol* 2005; **4:** 712–17.
11. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis. *J Child Neurol* 1999; **14:** 71–4.
12. Mackay MT, *et al.* Practice parameter: medical treatment of infantile spasms—report of the American Academy of Neurology and the Child Neurology Society. *Neurology* 2004; **62:** 1668–81.

Metabolic disorders. Vigabatrin, an irreversible inhibitor of GABA-transaminase, has been tried in GABA metabolic disorders, with or without concurrent epilepsy,[1-5] with ambivalent results. Data from 23 case reports of patients with succinic semialdehyde dehydrogenase deficiency indicated that vigabatrin was clinically beneficial in only about one-third of patients.[4]

1. Jaeken J, *et al.* Vigabatrin in GABA metabolism disorders. *Lancet* 1989; **i**: 1074.
2. Gibson KM, *et al.* Vigabatrin therapy in patient with succinic semialdehyde dehydrogenase deficiency. *Lancet* 1989; **ii:** 1105–6.
3. Stephenson JBP. Vigabatrin for startle-disease with altered cerebrospinal-fluid free gamma-aminobutyric acid. *Lancet* 1992; **340:** 430–1.
4. Gibson KM, *et al.* The clinical phenotype of succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria): case reports of 23 new patients. *Pediatrics* 1997; **99:** 567–74.
5. Leuzzi V, *et al.* Vigabatrin improves paroxysmal dystonia in succinic semialdehyde dehydrogenase deficiency. *Neurology* 2007; **68:** 1320–1.

Stiff-man syndrome. There have been anecdotal reports[1-3] of improvement of stiff-man syndrome (see under Muscle Spasm, p.993) with vigabatrin in patients unable to tolerate benzodiazepine therapy.

1. Vermeij FH, *et al.* Improvement of stiff-man syndrome with vigabatrin. *Lancet* 1996; **348:** 612.
2. Prevett MC, *et al.* Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1997; **48:** 1133–4.
3. Sharoqi IA. Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1998; **50:** 833–4.

Preparations

BP 2008: Vigabatrin Oral Powder; Vigabatrin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Sabril; ***Austral.:*** Sabril; ***Austria:*** Sabril; ***Belg.:*** Sabril; ***Braz.:*** Sabril; ***Canad.:*** Sabril; ***Chile:*** Sabril; ***Cz.:*** Sabril; ***Denm.:*** Sabrilex; ***Fin.:*** Sabrilex; ***Fr.:*** Sabril; ***Ger.:*** Sabril; ***Gr.:*** Sabril; ***Hong Kong:*** Sabril; ***Hung.:*** Sabril; ***Irl.:*** Sabril; ***Israel:*** Sabrilan; ***Ital.:*** Sabril; ***Mex.:*** Sabril; ***Neth.:*** Sabril; Sabrilex; ***Norw.:*** Sabrilex; ***NZ:*** Sabril; ***Pol.:*** Sabril; ***Port.:*** Sabril; ***S.Afr.:*** Sabril; ***Singapore:*** Sabril; ***Spain:*** Sabrilex; ***Swed.:*** Sabrilex; ***Switz.:*** Sabril; ***Turk.:*** Sabril; ***UK:*** Sabril.

Zonisamide *(BAN, USAN, rINN)*

AD-810; CI-912; PD-110843; Zonisamida; Zonisamidum. 1-(1,2-Benzoxazol-3-yl)methanesulphonamide.

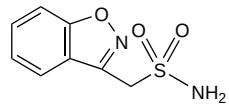
Зонизамид

$C_8H_8N_2O_3S$ = 212.2.

CAS — 68291-97-4.

ATC — N03AX15.

ATC Vet — QN03AX15.



Adverse Effects

The most common adverse effects with zonisamide have included anorexia, gastrointestinal disturbances such as abdominal pain, diarrhoea, and nausea, somnolence, dizziness, headache, ataxia, depression, and agitation or irritability. Severe, sometimes fatal, skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely. There have been isolated reports of aplastic anaemia, agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, and leucocytosis.

Other adverse effects have included renal calculi (see below), renal impairment, pancreatitis, rhabdomyolysis, abnormal liver function tests, psychosis, psychomotor slowing, reduced concentration, speech or language difficulties, paraesthesia, nystagmus, diplopia, weight loss, and fatigue. Reduced sweating with hyperthermia has occurred in children (see below).

Effects on mental function. For a review of the effects of antiepileptic therapy including zonisamide on *cognition* and *mood* (including the risk of suicidal ideation), see p.468.

Hyperthermia. Decreased sweating and hyperthermia have been reported in patients given zonisamide. By the end of December 2001 the manufacturers in the USA were aware of 40 such cases; of these, 38 had occurred in the first 11 years of marketing in Japan and 2 in the first year of marketing in the USA. Many cases were reported after exposure to high ambient temperatures and some progressed to heat stroke, but none had led to death.

The manufacturer noted that children appeared to be at an increased risk of developing these adverse reactions and should be monitored closely for such effects especially during warm or hot weather. Caution was also advised when zonisamide was given with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.[1]

1. O'Brien C [Elan Pharmaceuticals]. Important drug warning. Available at: http://www.fda.gov/medwatch/SAFETY/2002/Zonegran_deardoc.pdf (accessed 14/05/04)

Renal calculi. Patients treated with zonisamide in the USA and Europe may have had a higher incidence of renal calculi than those treated in Japan. In one US study,[1] 4 of 113 patients (3.5%) receiving long-term treatment with zonisamide developed renal calculi, but a familial relationship was found for 2. In pooled data[2] from earlier studies, renal calculi had been reported in 13 of 700 patients (1.9%) treated in the USA and Europe compared with 2 of 1008 patients (0.2%) in Japan. Another review,[3] involving information from more than 750 patients, considered the risk of renal calculi in zonisamide-treated patients to be 5 to 9 times greater than that in the general population. However, a later study[4] that evaluated all safety data available at the time (from the US and European clinical trial programme and the manufacturer's postmarketing surveillance database) found the prevalence of symptomatic renal calculi to be low. There has been a report[5] of 3 patients who developed renal calculi associated with zonisamide but were able to continue therapy with hydration and/or citrate supplementation.

1. Patsalos PN, Sander JWAS. Newer antiepileptic drugs: towards an improved risk-benefit ratio. *Drug Safety* 1994; **11:** 37–67.
2. Peters DH, Sorkin EM. Zonisamide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993; **45:** 760–87.
3. Bennett WM. Risk of kidney stones in patients treated with zonisamide. *Neurology* 2002; **58** (suppl 3): A298–A299.
4. Wroe S. Zonisamide and renal calculi in patients with epilepsy: how big an issue? *Curr Med Res Opin* 2007; **23:** 1765–73.
5. Richards KC, *et al.* Continued use of zonisamide following development of renal calculi. *Neurology* 2005; **64:** 763–4.

Precautions

Zonisamide is a sulfonamide derivative and is therefore contra-indicated in patients with a history of hypersensitivity to sulfonamides.

It should be used with care in patients with renal impairment; there is no data on safety in those with hepatic impairment. Zonisamide should be used with caution in patients who have risk factors for nephrolithiasis; adequate hydration is recommended to increase urine output, to try to reduce the risk of developing renal calculi, especially in predisposed patients.

Pancreatic lipase and amylase levels should be monitored in patients who develop pancreatitis and consideration should be given to withdrawing zonisamide. Patients who develop severe muscle pain or weakness, with or without fever, should have their serum creatine phosphokinase and aldolase levels assessed; if these are elevated, zonisamide may need to be withdrawn. A dietary supplement or increased food intake may be appropriate in patients who are losing weight or are underweight with zonisamide; withdrawing zonisamide may be warranted in those with substantial undesirable weight loss. Consideration should be given to withdrawing zonisamide in patients who develop unexplained rash.

Care is required when withdrawing zonisamide therapy—see also Uses and Administration below.

Breast feeding. Zonisamide is distributed into breast milk;[1] in view of the potential for serious adverse effects in infants from zonisamide, licensed product information recommends that it should only be used in nursing mothers if the benefits outweigh the risks. It is also recommended that breast feeding must not be resumed until 1 month after stopping zonisamide therapy. For comment on antiepileptic therapy and breast feeding, see p.467.

1. Kawada K, *et al.* Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; **24:** 95–7.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Pregnancy. Zonisamide crosses the placenta.[1] For comments on the management of epilepsy during pregnancy, see p.468.

1. Kawada K, *et al.* Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; **24:** 95–7.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Use with drugs that induce or inhibit the cytochrome P450 isoenzyme CYP3A4 may alter plasma concentrations of zonisamide. Carbamazepine, phenytoin, or phenobarbital reduce the half-life of zonisamide; reductions have also been noted with valproate but to a lesser degree.

The use of zonisamide with other drugs that cause nephrolithiasis should be avoided because of the increased risk of developing renal calculi (see under Adverse Effects, above). Caution is advised when zonisamide is used with other drugs known to cause heat-related disorders because of the increased risk of developing hyperthermia (see Adverse Effects, above).

◊ References.

1. Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007; **48:** 435–41.

Pharmacokinetics

Zonisamide is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within 2 to 6 hours of oral doses. Bioavailability is essentially complete; the presence of food does not affect the bioavailability of zonisamide but the time to reach peak plasma concentrations is delayed. Steady-state concentrations are achieved within 14 days. It is widely distributed into body tissues. Plasma protein binding is low (40 to 50%) but zonisamide is extensively bound to erythrocytes. The plasma elimination half-life is about 63 hours.

Zonisamide undergoes acetylation to *N*-acetylzonisamide and reduction mediated by the cytochrome P450 isoenzyme CYP3A4 to 2-sulfamoylacetylphenol (SMAP); both metabolites are inactive. Excretion is mainly in the urine; about 15 to 30% appearing as

unchanged drug, 15% as *N*-acetylzonisamide, and 50% as the glucuronide of SMAP.

Zonisamide crosses the placenta and is distributed into breast milk.

The pharmacokinetics of zonisamide are affected by use with other antiepileptics (see under Interactions, above).

◊ References.

1. Kochak GM, *et al.* Steady-state pharmacokinetics of zonisamide, an antiepileptic agent for treatment of refractory complex partial seizures. *J Clin Pharmacol* 1998; **38:** 166–71.
2. Mimaki T. Clinical pharmacology and therapeutic drug monitoring of zonisamide. *Ther Drug Monit* 1998; **20:** 593–7.
3. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. *Seizure* 2004; **13** (suppl 1): S5–S9.

Uses and Administration

Zonisamide, a benzisoxazole derivative, is used as an adjunctive antiepileptic in the treatment of partial seizures, with or without secondary generalisation.

In the UK, the usual initial oral dose in adults over 18 years of age is 50 mg daily in 2 divided doses, increased after 1 week to 100 mg daily. Thereafter, the dose may be further increased at weekly intervals by increments of up to 100 mg, to a usual dose of 300 to 500 mg daily, although some patients may respond to lower doses. Dose increments at intervals of 2 weeks should be considered in patients with hepatic or renal impairment and in patients who are not receiving CYP3A4 inducers (see also Interactions, above). Zonisamide may be given as a single dose or in 2 divided doses after the titration phase.

In the USA, the usual initial oral dose in patients over 16 years of age is 100 mg daily, increased after at least 2 weeks to 200 mg daily, given as a single dose or in 2 divided doses. Thereafter, if necessary, the dose may be further increased at intervals of at least 2 weeks by increments of 100 mg, to a dose of 400 mg daily. Doses up to 600 mg daily have been used, but there is no current evidence of an increase in response above 400 mg daily; many of the adverse effects of zonisamide are reported to be more frequent at doses of 300 mg daily and above.

As with other antiepileptics, withdrawal of zonisamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures; UK licensed product information has suggested that the dose may be decreased in steps of 100 mg at weekly intervals. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Bipolar disorder. Zonisamide may have psychotropic properties, and has been tried in the management of bipolar disorder (p.372).

References.

1. Baldassano CF, *et al.* Acute treatment of bipolar depression with adjunctive zonisamide: a retrospective chart review. *Bipolar Disord* 2004; **6:** 432–4.
2. Anand A, *et al.* A preliminary open-label study of zonisamide treatment for bipolar depression in 10 patients. *J Clin Psychiatry* 2005; **66:** 195–8.
3. McElroy SL, *et al.* Open-label adjunctive zonisamide in the treatment of bipolar disorders: a prospective trial. *J Clin Psychiatry* 2005; **66:** 617–24.
4. Ghaemi SN, *et al.* An open prospective study of zonisamide in acute bipolar depression. *J Clin Psychopharmacol* 2006; **26:** 385–8.
5. Wilson MS, Findling RL. Zonisamide for bipolar depression. *Expert Opin Pharmacother* 2007; **8:** 111–13.

Epilepsy. Zonisamide is used in the treatment of refractory epilepsy (p.465). Many studies have been conducted in Japan where clinical experience demonstrated its efficacy mainly in the treatment of partial seizures with or without secondary generalisation.[1,2] Data from studies[3-6] conducted outside Japan have confirmed the efficacy of zonisamide as an adjunct in the treatment of partial epilepsies. Efficacy in primary generalised and mixed-seizure epilepsies appears to be more variable, although it may be of value in refractory myoclonic seizures[7] and absence seizures.[8] Retrospective cohort studies[9,10] have also found that zonisamide may have efficacy as monotherapy. Zonisamide might also be of use in the treatment of epileptic syndromes such as Lennox-Gastaut syndrome,[11] and infantile spasms (as for example in West's syndrome), although only a small number of patients with the latter condition have been studied.[12,13]

1. Peters DH, Sorkin EM. Zonisamide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993; **45:** 760–87.
2. Patsalos PN, Sander JWAS. Newer antiepileptic drugs: towards an improved risk-benefit ratio. *Drug Safety* 1994; **11:** 37–67.
3. Leppik IE, *et al.* Efficacy and safety of zonisamide: results of a multicenter study. *Epilepsy Res* 1993; **14:** 165–73.
4. Schmidt D, *et al.* Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial. *Epilepsy Res* 1993; **15:** 67–73.
5. Chadwick DW, Marson AG. Zonisamide add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).
6. Brodie MJ, *et al.* Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures. *Epilepsia* 2005; **46:** 31–41.
7. Kyllerman M, Ben-Menachen E. Zonisamide for progressive myoclonus epilepsy: long-term observations in seven patients. *Epilepsy Res* 1998; **29:** 109–14.
8. Wilfong A, Schultz R. Zonisamide for absence seizures. *Epilepsy Res* 2005; **64:** 31–4.
9. Tosches WA, Tisdell J. Long-term efficacy and safety of monotherapy and adjunctive therapy with zonisamide. *Epilepsy Behav* 2006; **8:** 522–6.
10. Kothare SV, *et al.* Efficacy and safety of zonisamide monotherapy in a cohort of children with epilepsy. *Pediatr Neurol* 2006; **34:** 351–4.
11. You SJ, *et al.* Clinical efficacy of zonisamide in Lennox-Gastaut syndrome: Korean multicentric experience. *Brain Dev* 2008; **30:** 287–90.
12. Yanai S, *et al.* Treatment of infantile spasms with zonisamide. *Brain Dev* 1999; **21:** 157–61.
13. Lotze TE, Wilfong AA. Zonisamide treatment for symptomatic infantile spasms. *Neurology* 2004; **62:** 296–8.

Obesity. Anorexia and weight loss have been associated with zonisamide therapy (see Adverse Effects, above) and it has been tried, with some success, as an adjunct in the treatment of obesity[1,2] (p.2149); it has also been tried in binge-eating disorder associated with obesity.[3] Combination with bupropion (p.383) is under investigation.[2]

1. Gadde KM, *et al.* Zonisamide for weight loss in obese adults: a randomized controlled trial. *JAMA* 2003; **289:** 1820–5.
2. Gadde KM, *et al.* Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. *J Clin Psychiatry* 2007; **68:** 1226–9.
3. McElroy SL, *et al.* Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial. *J Clin Psychiatry* 2006; **67:** 1897–1906. Correction. *ibid.* 2007; **68:** 172.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Zonegran; ***Fr.:*** Zonegran; ***Ger.:*** Zonegran; ***Hung.:*** Zonegran; ***Irl.:*** Zonegran; ***Jpn:*** Excegran; ***Neth.:*** Zonegran; ***Port.:*** Zonegran; ***Spain:*** Zonegran; ***Swed.:*** Zonegran; ***UK:*** Zonegran; ***USA:*** Zonegran.

Amorolfine *(BAN, USAN, rINN)*

Amorolfiini; Amorolfin; Amorolfina; Amorolfinum; Ro-14-4767/000. (±)-*cis*-2,6-Dimethyl-4-[2-methyl-3-(*p*-*tert*-pentylphenyl)propyl]morpholine.

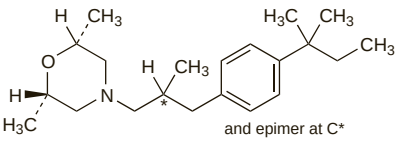
Аморольфин

$C_{21}H_{35}NO$ = 317.5.

CAS — 78613-35-1.

ATC — D01AE16.

ATC Vet — QD01AE16.



Amorolfine Hydrochloride *(BANM, rINNM)*

Amorolfine, Chlorhydrate d'; Amorolfini Hydrochloridum; Hidrocloruro de amorolfina; Ro-14-4767/002.

Аморольфина Гидрохлорид

$C_{21}H_{35}NO,HCl$ = 354.0.

CAS — 78613-38-4.

ATC — D01AE16.

ATC Vet — QD01AE16.

Adverse Effects

Skin irritation, presenting as erythema, pruritus, or a burning sensation, and, rarely, more severe skin reactions have been reported after topical application of amorolfine.

Antimicrobial Action

Amorolfine is a morpholine derivative with antifungal activity. It appears to act by interfering with the synthesis of sterols essential for the functioning of fungal cell membranes.

Amorolfine is active *in vitro* against a wide variety of pathogenic and opportunistic fungi including dermatophytes, *Blastomyces dermatitidis*, *Candida* spp., *Histoplasma capsulatum*, and *Sporothrix schenckii*. It also has variable activity against *Aspergillus* spp. However, despite its *in vitro* activity, amorolfine is inactive when given systemically and this limits its use to topical application for superficial infections.

Uses and Administration

Amorolfine is a morpholine derivative applied topically as the hydrochloride in the treatment of fungal nail and skin infections (p.521). After topical application, systemic absorption of amorolfine is negligible.

For the treatment of nail infections caused by dermatophytes, yeasts, and moulds a lacquer containing the equivalent of 5% amorolfine is painted onto the affected nail once or sometimes twice weekly until the nail has regenerated. Treatment generally needs to be continued for 6 to 12 months.

For skin infections, including dermatophyte infections, a cream containing the equivalent of 0.25% amorolfine is applied once daily for at least 2 to 3 weeks (up to 6 weeks for foot infections) and continued for 3 to 5 days after clinical cure is achieved.

◊ Reviews.

1. Haria M, Bryson HM. Amorolfine: a review of its pharmacological properties and therapeutic potential in the treatment of onychomycosis and other superficial fungal infections. *Drugs* 1995; **49:** 103–20.
2. Flagothier C, *et al.* New insights into the effect of amorolfine nail lacquer. *Mycoses* 2005; **48:** 91–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Loceryl; Locetar†; Micocide A; ***Austral.:*** Loceryl; ***Austria:*** Loceryl; ***Belg.:*** Loceryl; ***Braz.:*** Loceryl; ***Chile:*** Loceryl; ***Cz.:*** Loceryl; ***Denm.:*** Loceryl; ***Fin.:*** Loceryl; ***Fr.:*** Loceryl; ***Ger.:*** Loceryl; ***Gr.:*** Loceryl; ***Hong Kong:*** Loceryl; ***Hung.:*** Loceryl; ***Irl.:*** Loceryl; ***Ital.:*** Locetar; ***Jpn:*** Pekiron; ***Malaysia:*** Loceryl; ***Mex.:*** Loceryl; ***Norw.:*** Loceryl; ***NZ:*** Loceryl; ***Philipp.:*** Locetar; ***Pol.:*** Loceryl; ***Port.:*** Locetar; ***Rus.:*** Loceryl (Лоцерил); ***S.Afr.:*** Loceryl; ***Singapore:*** Loceryl; ***Spain:*** Locetar; Odenil; ***Swed.:*** Loceryl; ***Switz.:*** Loceryl; ***UK:*** Curanail; Loceryl; ***Venez.:*** Loceryl.

Amphotericin B *(BANM, rINN)*

Amfotericin; Amfotericin B; Amfotericina B; Amfotericinas B; Amforterisiini; Amforterisiini B; Amforterisin; Amforterisin B; Amfoterycyna b; Amphotericin; Amphotéricine B; Amphotericinum; Amphotericinum B; Anfotericina B.

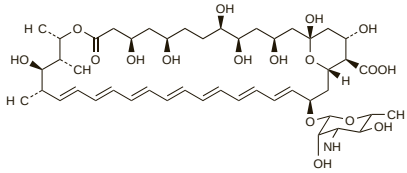
Амфотерицин В

$C_{47}H_{73}NO_{17}$ = 924.1.

CAS — 1397-89-3.

ATC — A01AB04; A07AA07; G01AA03; J02AA01.

ATC Vet — QA01AB04; QA07AA07; QG01AA03; QJ02AA01.



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

Ph. Eur. 6.2 (Amphotericin B; Amphotericin BP 2008). A mixture of antifungal polyenes produced by the growth of certain strains of *Streptomyces nodosus* or by any other means. It consists largely of amphotericin B. It occurs as a yellow or orange powder. The potency is not less than 750 units per mg with reference to the dried substance. It contains not more than 10% of tetraenes, or not more than 5% if intended for use in parenteral dosage forms. Practically insoluble in water and in alcohol; soluble in dimethyl sulfoxide and in propylene glycol; slightly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Amphotericin B is inactivated at low pH values. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Amphotericin B). A yellow to orange, odourless or practically odourless, powder. It contains not less than 750 micrograms of $C_{47}H_{73}NO_{17}$ per mg, and, for material intended for oral or topical use, not more than 15% of amphotericin A, both calculated on the dried substance. Insoluble in water, in dehydrated alcohol, in ether, in benzene, and in toluene; soluble in dimethylformamide, in dimethyl sulfoxide, and in propylene glycol; slightly soluble in methyl alcohol. Store at a temperature not exceeding 8° in airtight containers. Protect from light.

◊ References.

1. Kintzel PE, Smith GH. Practical guidelines for preparing and administering amphotericin B. *Am J Hosp Pharm* 1992; **49:** 1156–64.

Formulation. Conventional formulations of amphotericin B injection are typically a complex of amphotericin B and deoxycholate with suitable buffers which form a colloidal dispersion when reconstituted. Nonconventional '**lipid**' formulations of amphotericin B for injection include liposomal amphotericin B, a colloidal dispersion of an amphotericin B and sodium cholesteryl sulfate complex, and a phospholipid complex.

Incompatibility. Because of the wide range of incompatibilities reported with conventional and lipid formulations of amphotericin B, it is generally advisable not to mix them with any other drug. Most incompatibilities are caused by precipitation of amphotericin B due to a change in pH or by the disruption of the colloidal suspension. Precipitation can occur if amphotericin B is added to sodium chloride 0.9% or to electrolyte solutions.

Although heparin is generally reported to be compatible with conventional amphotericin B injection, care should be taken if heparin flush solutions, which are diluted with sodium chloride solution, are used to maintain the patency of intravenous lines in patients receiving amphotericin B. Flushing the intravenous line with 5% glucose solution has been suggested.

Mixtures of conventional amphotericin B in commercial lipid emulsions have been reported to be unstable,[1-3] although others have reported satisfactory stability.[4-6] In one study,[6] vigorous agitation of the mixtures enhanced their stability when compared with gentle mixing.

1. Ericsson O, *et al.* Amphotericin B is incompatible with lipid emulsions. *Ann Pharmacother* 1996; **30:** 298.
2. Ranchère JY, *et al.* Amphotericin B intralipid formulation: stability and particle size. *J Antimicrob Chemother* 1996; **37:** 1165–9.
3. Heide PE. Precipitation of amphotericin B from iv fat emulsion. *Am J Health-Syst Pharm* 1997; **54:** 1449.
4. Lopez RM, *et al.* Stability of amphotericin B in an extemporaneously prepared iv fat emulsion. *Am J Health-Syst Pharm* 1996; **53:** 2724–7.
5. Owens D, *et al.* Stability of amphotericin B 0.05 and 0.5 mg/mL in 20% fat emulsion. *Am J Health-Syst Pharm* 1997; **54:** 683–6.
6. Shadkhan Y, *et al.* The use of commercially available lipid emulsions for the preparation of amphotericin B-lipid admixtures. *J Antimicrob Chemother* 1997; **39:** 655–8. Correction. *ibid.* 1998; **42:** 413.

Preparation of solutions for injection. Recommendations from the manufacturers for preparation of amphotericin solutions are:

- *conventional amphotericin B* formulations for injection are prepared by reconstitution of amphotericin B with sterile water for injection without preservatives, then dilution with glucose injection 5% with a pH above 4.2 to the desired final concentration.
- *liposomal amphotericin B*: injections are prepared by reconstitution with sterile water for injection without a preservative; the required reconstituted amount is then withdrawn and injected via a sterile filter into the desired volume of glucose 5%.
- *amphotericin B-sodium cholesteryl sulfate complex*: injections are prepared by rapidly adding the required amount of water for injection, then further diluting with glucose 5% until the desired final concentration is reached.
- *amphotericin B-phospholipid complex*: before infusion the suspension concentrate must be diluted to the required final concentration with glucose 5%. The required amount of concentrate is injected via a sterile filter into the glucose 5%.

CAUTION: Mixture with sodium chloride injection 0.9% would precipitate amphotericin B.

Stability of oral suspensions. An oral suspension of amphotericin B 100 mg/mL, prepared from powder and a cherry-flavoured vehicle and maintained at pH 5.3, was found to be stable at 22 to 25° for 93 days.[1]

1. Dentinger PJ, *et al.* Stability of amphotericin B in an extemporaneously compounded oral suspension. *Am J Health-Syst Pharm* 2001; **58:** 1021–4.

Adverse Effects

Amphotericin B for intravenous use was originally only available in a conventional colloidal form; lipid formulations have been developed to reduce toxicity. The following adverse effects apply to the **conventional** form. Common adverse effects which occur during or after intravenous infusion of amphotericin B include headache, nausea, vomiting, chills, fever, malaise, muscle and joint pains, anorexia, diarrhoea, and gastrointestinal cramp. Hypertension, hypotension, cardiac arrhythmias including ventricular fibrillation and cardiac arrest, skin rashes, flushing, anaphylactoid reactions including bronchospasm and dyspnoea, blurred vision, tinnitus, hearing loss, vertigo, gastrointestinal bleeding, liver disorders, peripheral neuropathy, and convulsions have been reported occasionally.

Some degree of nephrotoxicity occurs in almost all patients given amphotericin B intravenously. Both tubular and glomerular damage occur; there may be improvement on cessation of therapy, but there is a risk of permanent renal impairment, particularly in patients given large cumulative doses (over 5 g). Renal tubular acidosis without systemic acidosis may develop. Use of amphotericin B is associated with increased urinary excretion of potassium and magnesium resulting in hypokalaemia and hypomagnesaemia respectively. Uric acid excretion is increased and nephrocalcinosis can occur. Limited data indicate that renal toxicity may be associated with sodium depletion; for strategies to improve sodium load see Nephrotoxicity, under Treatment of Adverse Effects, below.

A reversible, normocytic, normochromic anaemia develops in most patients given amphotericin B, possibly due to a direct suppressive effect on erythropoietin production. There are rare reports of thrombocytopenia, leucopenia, agranulocytosis, eosinophilia, and coagulation defects.

Leukoencephalopathy has been reported rarely in patients also receiving total body irradiation.

Amphotericin B solutions irritate the venous endothelium and may cause pain and thrombophlebitis at the injection site. Extravasation may cause tissue damage.

After intrathecal injection amphotericin B may also cause irritation of the meninges, neuropathy with pain, impaired vision, and retention of urine.

In general, adverse effects of **lipid** formulations have been similar to those of conventional amphotericin B, but are less frequent and less severe. Brief reversible episodes of renal impairment have been observed but these formulations have been considered to be safe enough to use in patients with renal impairment who