dia, sino-atrial block, second- or third-degree AV block, or Stokes-Adams syndrome.

Burning, itching, and paraesthesia, particularly in the groin area, have also been reported after intravenous fosphenytoin; reducing the rate of, or temporarily stopping, the infusion may relieve the discomfort.

Caution should be exercised when giving fosphenytoin to patients in whom phosphate restriction is necessary. The rate of metabolism of fosphenytoin to phenytoin may be increased in patients with hepatic or renal disease, or in those with hypoalbuminaemia, and consequently there is an increased risk of adverse effects in such patients.

Effects on the cardiovascular system. The UK CSM[1] stated in May 2000 that worldwide there had been reports of 21 cases of asystole, ventricular fibrillation, or cardiac arrest associated with intravenous use of fosphenytoin. Of these, 5 cases had received doses or infusion rates greater than recommended. There had also been 34 reports of hypotension, 15 of bradycardia, and 10 of varying degrees of heart block. Most reactions had occurred within 30 minutes of the infusion. A review[2] of adverse events associated with fosphenytoin infusion received by the FDA Adverse Event Reporting System between 1997 and 2002 identified 29 of adverse cardiac events, including 10 fatalities. Of these reports, 5 were of sinus arrest, 4 of AV block, and 8 of asystole. The authors acknowledged that the majority of patients had serious confounders including renal failure, stroke, acute cardiac ischaemia or failure, overdose, or infection.

ECG changes consistent with hypocalcaemia have occurred in a patient who received 1500 mg-equivalents of phenytoin over 85 minutes as an intravenous infusion of fosphenytoin.[3] The patient had initially been normocalcaemic and it was suggested that the effect may have been due to acute inorganic phosphate toxicity.

1. Committee on Safety of Medicines/Medicines Control Agency. Fosphenytoin sodium (Pro-Epanutin): serious arrhythmias and hypotension. *Current Problems* 2000; **26:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
2. Adams BD, *et al*. Fosphenytoin may cause hemodynamically unstable bradydysrhythmias. *J Emerg Med* 2006; **30:** 75–9.
3. Keegan MT, *et al.* Hypocalcemia-like electrocardiographic changes after administration of intravenous fosphenytoin. *Mayo Clin Proc* 2002; **77:** 584–6.

Porphyria. Phenytoin is considered unsafe in porphyric patients; it would be prudent to assume that this consideration also applied to its prodrug, fosphenytoin.

Interactions

As for Phenytoin, p.497.

Pharmacokinetics

Plasma concentrations of fosphenytoin are maximal at the end of intravenous infusion and about 30 minutes after intramuscular injection. Protein binding of fosphenytoin is high (95 to 99%), mainly to albumin, and is saturable. Fosphenytoin displaces phenytoin from protein binding sites which increases the fraction of unbound phenytoin to up to 30% for about half to one hour post-infusion. Fosphenytoin is rapidly and completely hydrolysed to phenytoin with a conversion half-life of about 15 minutes; one mmol of fosphenytoin yields one mmol of phenytoin, and the same of phosphate and formate. Metabolites of phenytoin are excreted in the urine. For the pharmacokinetics of phenytoin, see p.500.

◊ References.

1. Fischer JH, *et al.* Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet* 2003; **42:** 33–58.

Uses and Administration

Fosphenytoin is a prodrug of phenytoin (p.495) used similarly as part of the emergency treatment of status epilepticus (p.469). It is also used for the prevention and treatment of post-traumatic seizures (p.501) associated with neurosurgery or head trauma and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy (p.465).

Fosphenytoin is given as the sodium salt and doses of fosphenytoin sodium are expressed as phenytoin sodium equivalents (PSE); therefore no adjustment in dosage is necessary when substituting fosphenytoin for phenytoin or vice versa. Fosphenytoin may be given by intramuscular injection or intravenous infusion; only the intravenous route is recommended in children.

The maximum rate of intravenous infusion in PSE is 150 mg/minute and should not be exceeded. Continuous monitoring of ECG, blood pressure, and respiratory function is recommended during intravenous infusion. Patients should also be observed for at least 30 minutes after the end of infusion.

In the treatment of tonic-clonic status epilepticus a benzodiazepine such as diazepam or lorazepam is usually given initially intravenously or rectally followed by fosphenytoin. In the UK, the loading dose in PSE is 15 mg/kg given as a single dose by intravenous infusion at a rate of 100 to 150 mg/minute. The intramuscular route is not appropriate for the management of status epilepticus because peak phenytoin concentrations will not be reached quickly enough. The loading dose for seizures other than in status epilepticus is 10 to 15 mg/kg given as a single dose by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Initial maintenance doses for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 or 2 divided doses by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given intramuscularly or by intravenous infusion at a rate of 50 to 100 mg/minute may be substituted for oral phenytoin at the same equivalent total daily dose for up to 5 days.

In the USA, loading doses in PSE of up to 20 mg/kg are permitted, and initial maintenance doses are 4 to 6 mg/kg daily.

For doses in children, see below.

A lower loading dose and/or infusion rate, and lower or less frequent maintenance dosing may be necessary for elderly patients; UK licensed product information suggests a reduction in dose or rate of 10 to 25%. Similar reductions are suggested for patients with renal or hepatic impairment (see also below) or in those with hypoalbuminaemia, except in the treatment of status epilepticus.

◊ References.

1. Wilder BJ, *et al.* Safety and tolerance of multiple doses of intramuscular fosphenytoin substituted for oral phenytoin in epilepsy or neurosurgery. *Arch Neurol* 1996; **53:** 764–8.
2. Meek PD, *et al.* Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. *Arch Intern Med* 1999; **159:** 2639–44.
3. Heafield MTE. Managing status epilepticus: new drug offers real advantages. *BMJ* 2000: **320:** 953–4.
4. DeToledo JC, Ramsay RE. Fosphenytoin and phenytoin in patients with status epilepticus: improved tolerability versus increased costs. *Drug Safety* 2000; **22:** 459–66.

Administration in children. In the UK, fosphenytoin sodium may be given to children over 5 years of age for the emergency treatment of status epilepticus, the prevention and treatment of post-traumatic seizures associated with neurosurgery or head trauma, and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy. It is given by intravenous infusion and doses are expressed as phenytoin sodium equivalents (PSE).

In the treatment of tonic-clonic status epilepticus, the loading dose in PSE is 15 mg/kg given as a single dose at a rate of 2 to 3 mg/kg per minute; however, the *BNFC* allows up to 20 mg/kg. In the treatment or prophylaxis of seizures other than in status epilepticus, the loading dose in PSE is 10 to 15 mg/kg given as a single dose at a rate of 1 to 2 mg/kg per minute. The maximum rate of infusion of loading doses is 3 mg/kg per minute or 150 mg/minute and should not be exceeded. Initial maintenance doses in PSE for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 to 4 divided doses at a rate of 1 to 2 mg/kg per minute, not exceeding 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given at a rate of 1 to 2 mg/kg per minute, not exceeding 50 to 100 mg/minute, may be substituted for oral phenytoin at equivalent total daily doses for up to 5 days.

Similar precautions to those in adults apply to the monitoring of clinical parameters and plasma-phenytoin concentrations in children (see above).

Administration in hepatic or renal impairment. The rate and extent of conversion of fosphenytoin to phenytoin in patients with hepatic cirrhosis or renal impairment requiring dialysis was not found to be significantly different from those for healthy controls.[1] However, there was a trend towards an increase in fosphenytoin clearance and a decrease in the time to peak phenytoin concentrations in those with hepatic or renal impairment. Consequently, the authors recommended that fosphenytoin may need to be given at lower doses or infused more slowly (see above for the licensed product recommendations).

1. Aweeka FT, *et al.* Pharmacokinetics of fosphenytoin in patients with hepatic or renal disease. *Epilepsia* 1999; **40:** 777–82.

Preparations

USP 31: Fosphenytoin Sodium Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Pro-Epanutin†; ***Austria:*** Pro-Epanutin; ***Canad.:*** Cerebyx; ***Denm.:*** Pro-Epanutin; ***Fin.:*** Pro-Epanutin; ***Fr.:*** Prodilantin; ***Gr.:*** Pro-Epanutin; ***Irl.:*** Pro-Epanutin; ***Neth.:*** Pro-Epanutin†; ***Norw.:*** Pro-Epanutin; ***Spain:*** Cereneu; ***Swed.:*** Pro-Epanutin; ***UK:*** Pro-Epanutin; ***USA:*** Cerebyx.

Gabapentin *(BAN, USAN, rINN)*

CI-945; Gabapentiini; Gabapentina; Gabapentine; Gabapentinum; GOE-3450. 1-(Aminomethyl)cyclohexaneacetic acid.

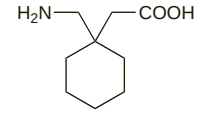
Габапентин

$C_9H_{17}NO_2$ = 171.2.

CAS — 60142-96-3.

ATC — N03AX12.

ATC Vet — QN03AX12.



Pharmacopoeias. In *US.*

USP 31 (Gabapentin). A white to off-white, crystalline solid. Freely soluble in water and in alkaline and acidic solutions. A 2% solution in water has a pH of 6.5 to 8.0.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with gabapentin are somnolence, dizziness, ataxia, and fatigue. Nystagmus, tremor, diplopia, amblyopia, pharyngitis, rhinitis, dysarthria, nausea and vomiting, weight gain, oedema, dyspepsia, amnesia, weakness, paraesthesia, arthralgia, purpura, leucopenia, anxiety, and urinary-tract infection may occur less frequently. Rarely, pancreatitis, altered liver function tests, erythema multiforme, Stevens-Johnson syndrome, myalgia, headache, and blood glucose fluctuations in diabetics have been reported. Common psychiatric effects include confusion, depression, and nervousness, and, more rarely, hallucinations and psychoses. Other adverse effects include acute renal failure, allergic reactions, alopecia, angioedema, chest pain, hepatitis, jaundice, movement disorders such as choreoathetosis, dyskinesia and dystonia, palpitations, thrombocytopenia, and tinnitus.

Gabapentin should be used with caution in patients with renal impairment and in those undergoing haemodialysis. False positive readings have been reported with some urinary protein tests in patients taking gabapentin.

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

Incidence of adverse effects. A postmarketing surveillance study[1] of 3100 patients taking gabapentin identified drowsiness or sedation as the most frequent adverse effect, occurring in about 6.7%. The incidences of other adverse effects were: headache, 3.6%; fatigue, 3.5%; nausea and vomiting, 2.6%; and dizziness, 2.4%. Less common adverse events included rash, visual defect, and ataxia. Overall, adverse effects were reported as the reason for stopping treatment in about 10% of patients. In the 136 children aged under 12 years whose data were included in the study, the most frequently reported treatment-related adverse events were eczema, rash, and vomiting. In this study, none of the 11 infants born to mothers taking gabapentin throughout pregnancy had congenital abnormalities.

1. Wilton LV, Shakir S. A postmarketing surveillance study of gabapentin as add-on therapy for 3,100 patients in England. *Epilepsia* 2002; **43:** 983–92.

Breast feeding. For mention of the pharmacokinetics of gabapentin during pregnancy and breast feeding, see under Pharmacokinetics, below.

For comment on antiepileptic therapy and breast feeding, see p.467.

Carcinogenicity. It had been reported[1] that studies on gabapentin had been temporarily stopped in 1990 when pancreatic tumours were seen in *rodent* studies. However, the tumours were benign, occurred only with large doses, and were not thought to relate to humans.

1. Ramsay RE. Clinical efficacy and safety of gabapentin. *Neurology* 1994; **44** (suppl 5): S23–S30.

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

Effects on bone. For the effects of antiepileptics on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on the liver. A report[1] of a patient who developed cholestatic jaundice 2 weeks after starting therapy with gabapentin 300 mg three times daily for diabetic neuropathy. Clinical symptoms and liver function tests improved on withdrawal of gabapentin.

1. Richardson CE, *et al.* Gabapentin induced cholestasis. *BMJ* 2002; **325:** 635.

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

Effects on the skin. For a suggestion that skin reactions are less common with gabapentin than with some other antiepileptics see under Phenytoin, p.496.

Overdosage. A 16-year-old girl complained of dizziness 6 hours after ingesting 48.9 g of gabapentin and was lethargic but arousable 2 hours later.[1] Her gabapentin plasma concentration was 62 micrograms/mL 8.5 hours after ingestion. By 18 hours she was alert and had no further complaints of lethargy or dizziness. In another report[2] a patient with renal failure inadvertently received inappropriately high doses of gabapentin for 3 weeks and had a serum gabapentin concentration of 85 micrograms/mL without serious adverse effects. However, a patient with end-stage renal disease who twice took extra doses of gabapentin between haemodialysis sessions developed marked somnolence and hypoxia severe enough to require intubation on both occasions; haemodialysis produced rapid improvement.[3] A prospective observational study[4] of gabapentin exposures reported to 3 poison centers has described a case series of 20 patients who took from 50 mg to 35 g of gabapentin alone. Of these, 12 experienced clinical symptoms including drowsiness, dizziness, gastrointestinal disturbance, hypotension, and mild tachycardia. These effects developed in under 5 hours and lasted for less than 24 hours; toxicity was generally mild and there were no fatalities.

1. Fischer JH, *et al.* Lack of serious toxicity following gabapentin overdose. *Neurology* 1994; **44:** 982–3.
2. Verma A, *et al.* A case of sustained massive gabapentin overdose without serious side effects. *Ther Drug Monit* 1999; **21:** 615–17.
3. Jones H, *et al.* Gabapentin toxicity requiring intubation in a patient receiving long-term hemodialysis. *Ann Intern Med* 2002; **137:** 74.
4. Klein-Schwartz W, *et al.* Characterization of gabapentin overdose using a poison center case series. *J Toxicol Clin Toxicol* 2003; **41:** 11–15.

Pregnancy. For mention of the pharmacokinetics of gabapentin during pregnancy and breast feeding, see under Pharmacokinetics, below.

For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

The absorption of gabapentin from the gastrointestinal tract is reduced by antacids containing aluminium with magnesium; it is recommended that gabapentin is taken at least 2 hours after any such antacid. Morphine has been reported to reduce the clearance of gabapentin; patients receiving both drugs should be monitored for signs of CNS depression and doses should be reduced accordingly. Cimetidine has also been reported to reduce the renal clearance of gabapentin but licensed product information does not consider this to be of clinical importance. For references to possible interactions with other antiepileptics, see under Phenytoin, p.498 and under Felbamate, p.481.

Pharmacokinetics

Gabapentin is absorbed from the gastrointestinal tract by means of a saturable mechanism. After multiple dosing peak plasma concentrations are usually achieved within 2 to 3 hours of a dose and steady state achieved within 1 to 2 days. Gabapentin is not appreciably metabolised and most of a dose is excreted unchanged in the urine with the remainder appearing in the faeces. Gabapentin is widely distributed throughout the body but binding to plasma proteins is minimal. The elimination half-life has been reported to be about 5 to 7 hours. Gabapentin is distributed into breast milk.

◊ References.

1. Blum RA, *et al.* Pharmacokinetics of gabapentin in subjects with various degrees of renal function. *Clin Pharmacol Ther* 1994; **56:** 154–9.
2. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
3. Berry DJ, *et al.* The absorption of gabapentin following high dose escalation. *Seizure* 2003; **12:** 28–36.

Children. A study[1] of the pharmacokinetics of single doses of gabapentin in healthy children aged 1 month to 12 years found that peak plasma concentrations occurred 2 to 3 hours after the dose in all age groups but that the mean value was higher in those older than 5 years than in younger children, and the exposure was calculated to be about 30% less in the younger age group. As a result it was suggested that the initial dose of gabapentin in studies of safety and efficacy should be 40 mg/kg daily in children aged from 1 month up to 5 years, and 30 mg/kg daily in children aged 5 to 12 years. (For licensed doses, see Administration in children, below.) A pharmacokinetics study[2] in children with uncontrolled seizures (aged from 3 to about 15 years) also found a markedly higher mean oral clearance of gabapentin when compared with adults.

1. Haig GM, *et al.* Single-dose gabapentin pharmacokinetics and safety in healthy infants and children. *J Clin Pharmacol* 2001; **41:** 507–14.
2. Tallian KB, *et al.* Pharmacokinetics of gabapentin in paediatric patients with uncontrolled seizures. *J Clin Pharm Ther* 2004; **29:** 511–15.

Pregnancy and breast feeding. The pharmacokinetics of gabapentin were studied[1] in 6 women, and in their offspring, during pregnancy, delivery, and breast feeding. Findings suggested that gabapentin is actively transported across the placenta and accumulates in the fetus although its effect was unclear. All the deliveries, including one preterm, were uneventful and all of the infants were healthy, apart from one who became cyanosed and mildly hypotonic 8 hours after birth.

The distribution of gabapentin into breast milk was extensive and neonates were found to have a lower capacity to eliminate gabapentin than adults, with an elimination half-life of about 14 hours. However, the plasma concentrations in the breast-fed infants appeared to be low and the relative infant dose was estimated to be 1.3 to 3.8% of the mothers' weight-adjusted dose at 0.2 to 1.3 mg/kg daily. No adverse effects were reported in the infants, and the authors considered that gabapentin was generally safe during breast feeding.

1. Öhman I, *et al.* Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? *Epilepsia* 2005; **46:** 1621–4.

Uses and Administration

Gabapentin is an antiepileptic used as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. It is not generally considered effective for absence seizures. Although gabapentin is an analogue of gamma-aminobutyric acid (GABA), it is neither a GABA agonist nor antagonist and its mechanism of action is unknown. Gabapentin is also used in the treatment of neuropathic pain.

In the UK, the initial oral dose of gabapentin for the treatment of **epilepsy** is 300 mg on the first day of treatment, 300 mg twice daily on the second day, and 300 mg three times daily on the third day; thereafter the dose may be increased in increments of 300 mg every 2 to 3 days until effective antiepileptic control is achieved, which is usually within the range of 0.9 to 3.6 g daily. Higher doses up to a maximum of 4.8 g daily have been reported to be well tolerated. Similar doses are used in the USA. The total daily dose should be taken in three equally divided doses and the maximum dosage interval should not exceed 12 hours.

For details of doses in children, see below.

In the treatment of **neuropathic pain**, doses should be titrated to a usual maximum of 1.8 g daily in three divided doses, in a similar manner to that recommended above for the treatment of epilepsy. Higher doses have sometimes been given.

As with other antiepileptics, withdrawal of gabapentin 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. Licensed product information recommends reducing the dose gradually over at least 7 days. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Dosage of gabapentin should be reduced in patients with renal impairment (see below).

Gabapentin enacarbil (XP-13512) has been investigated as a prodrug of gabapentin.

Administration in children. In the UK, for the treatment of partial seizures with or without secondary generalisation, gabapentin is licensed for use as adjunctive therapy in children aged 6 years and over and as monotherapy in those aged 12 years and over. As *adjunctive therapy*, gabapentin may be given in an initial oral dose of 10 to 15 mg/kg daily, titrated over a period of about 3 days until effective antiepileptic control is achieved, which is usually within the range 25 to 35 mg/kg daily. Higher doses up to a maximum of 50 mg/kg daily have been reported to be well tolerated. Although not licensed for use in younger children, the *BNFC* suggests that similar initial doses may be used in those aged 2 to 12 years; maintenance doses of 10 to 20 mg/kg 3 times daily (up to 900 mg daily for children weighing 36 kg or under, or 1.2 g daily for those over 36 kg) are also recommended. Older children may be given the usual adult dosage regimen (see above) titrated to a maximum of 2.4 g daily. When used as *monotherapy*, the usual adult dosage regimen is given.

In the USA, gabapentin is licensed for *adjunctive* use in children aged 3 years and over. Initial doses are as for the UK; the maintenance dose for children aged 3 to 4 years is 40 mg/kg daily, and for those aged 5 years and over is 25 to 35 mg/kg daily. Children aged 12 years and over may be given the usual adult dosage regimen (see above).

The total daily dose should be taken in 3 equally divided doses and the maximum dosage interval should not exceed 12 hours.

For a pharmacokinetic study suggesting that initial doses in younger children should be proportionately higher than in older ones, see above.

Administration in renal impairment. Reduced doses of gabapentin are recommended for patients with renal impairment or those undergoing haemodialysis. Licensed UK product information recommends the following maintenance doses based on creatinine clearance (CC) and given as 3 divided doses:

- CC 50 to 79 mL/minute: 600 to 1800 mg daily
- CC 30 to 49 mL/minute: 300 to 900 mg daily
- CC 15 to 29 mL/minute: 300 mg on alternate days to 600 mg daily
- CC less than 15 mL/minute: 300 mg on alternate days to 300 mg daily

For those undergoing haemodialysis who have never received gabapentin, the recommended loading dose is 300 to 400 mg followed by 200 to 300 mg after each 4 hours of haemodialysis. On dialysis-free days no doses of gabapentin should be given (see also Overdosage, above).

Ciguatera poisoning. Gabapentin has relieved some of the neurological symptoms associated with ciguatera poisoning (see Mannitol, p.1331).

Epilepsy. Gabapentin is used in epilepsy (p.465) as adjunctive therapy for partial seizures with or without secondary generalisation in patients refractory to standard antiepileptics. In double-blind placebo-controlled studies[1-4] in such patients seizure frequency was reduced when gabapentin was added to treatment. Long-term efficacy has been encouraging,[5-7] and its lack of potential for interactions with other antiepileptics is considered to make it particularly suitable for adjunctive treatment. Dosage is adjusted against clinical response rather than by monitoring blood concentrations. Gabapentin is also used as monotherapy in partial epilepsy;[8-10] its efficacy as adjunctive treatment in generalised seizures remains to be determined.

Gabapentin has been found to be effective as adjunctive therapy in children with refractory partial seizures.[11]

1. UK Gabapentin Study Group. Gabapentin in partial epilepsy. *Lancet* 1990; **335:** 1114–17.
2. Sivenius J, *et al.* Double-blind study of gabapentin in the treatment of partial seizures. *Epilepsia* 1991; **32:** 539–42.
3. US Gabapentin Study Group. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. *Neurology* 1993; **43:** 2292–8.
4. Anhut H, *et al.* International Gabapentin Study Group. Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. *Epilepsia* 1994; **35:** 795–801.
5. US Gabapentin Study Group. The long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in drug-resistant partial epilepsy. *Epilepsy Res* 1994; **18:** 67–73.
6. Sivenius J, *et al.* Long-term study with gabapentin in patients with drug-resistant epileptic seizures. *Arch Neurol* 1994; **51:** 1047–50.
7. Anhut H, *et al.* Long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in patients with refractory partial seizures. *J Epilepsy* 1995; **8:** 44–50.
8. Ojemann LM, *et al.* Long-term treatment with gabapentin for partial epilepsy. *Epilepsy Res* 1992; **13:** 159–65.

9. Beydoun A, *et al.* Gabapentin monotherapy II: a 26-week, double-blind, dose-controlled multicenter study of conversion from polytherapy in outpatients with refractory complex partial or secondarily generalized seizures. *Neurology* 1997; **49:** 746–52.
10. Chadwick DW, *et al.* A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. *Neurology* 1998; **51:** 1282–8.
11. Appleton R, *et al.* Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study. *Epilepsia* 1999; **40:** 1147–54.

Headache. Benefit has been reported[1] from the use of gabapentin in the prophylaxis of *migraine* (p.616). Gabapentin may also be effective[2,3] in the management of *cluster headache* (p.616), and has been tried[4] in the prophylaxis of *chronic daily headache.*

1. Mathew NT, *et al.* Efficacy of gabapentin in migraine prophylaxis. *Headache* 2001; **41:** 119–128.
2. Leandri M, *et al.* Drug-resistant cluster headache responding to gabapentin: a pilot study. *Cephalalgia* 2001; **21:** 744–6.
3. Schuh-Hofer S, *et al.* The use of gabapentin in chronic cluster headache patients refractory to first-line therapy. *Eur J Neurol* 2007; **14:** 694–6.
4. Spira PJ, Beran RG. Australian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology* 2003; **61:** 1753–9.

Hiccup. Gabapentin has been tried[1,2] in the treatment of hiccups (p.976).

1. Hernández JL, *et al.* Gabapentin for intractable hiccup. *Am J Med* 2004; **117:** 279–81.
2. Alonso-Navarro H, *et al.* Refractory hiccup: successful treatment with gabapentin. *Clin Neuropharmacol* 2007; **30:** 186–7.

Hot flushes. Gabapentin appears to be of benefit in the management of hot flushes associated with treatment of breast cancer (p.661); a study involving 420 women with breast cancer experiencing hot flushes (excluding women on active chemotherapy, but most of whom were receiving adjuvant endocrine therapy), found that a dose of 900 mg daily in three divided doses for 8 weeks was effective, although a dose of 300 mg daily was not.[1]

There is also evidence of benefit[2,3] from gabapentin in the same dose (900 mg daily) in women experiencing hot flushes as a symptom of the menopause (p.2077). Another randomised placebo-controlled study[4] found gabapentin 2.4 g daily to be as effective as conjugated oestrogens 625 micrograms daily in the treatment of hot flushes in postmenopausal women.

1. Pandya KJ, *et al.* Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005; **366:** 818–24.
2. Guttuso T, *et al.* Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003; **101:** 337–45.
3. Loprinzi CL, *et al.* Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. *J Clin Oncol* 2007; **25:** 308–12.
4. Reddy SY, *et al.* Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. *Obstet Gynecol* 2006; **108:** 41–8.

Lesch-Nyhan syndrome. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome (p.976) has been reported to improve in those given antiepileptics such as gabapentin.[1]

1. McManaman J, Tam DA. Gabapentin for self-injurious behavior in Lesch-Nyhan syndrome. *Pediatr Neurol* 1999; **20:** 381–2.

Motor neurone disease. Interest has been shown in gabapentin as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p.2380) because it may inhibit glutamate formation. Results from an early study[1] demonstrated a trend towards a beneficial effect; however, a randomised trial[2] failed to confirm any benefit from gabapentin on disease progression or symptoms.

1. Miller RG, *et al.* Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 1996; **47:** 1383–8.
2. Miller RG, *et al.* Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 2001; **56:** 843–8.

Multiple sclerosis. Gabapentin has been found to control pain, spasm, and spasticity in patients with multiple sclerosis (p.892).[1-6] It may also be of benefit in acquired nystagmus secondary to multiple sclerosis.[7]

1. Mueller ME, *et al.* Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. *Arch Phys Med Rehabil* 1997; **78:** 521–4.
2. Samkoff LM, *et al.* Amelioration of refractory dysesthetic limb pain in multiple sclerosis by gabapentin. *Neurology* 1997; **49:** 304–5.
3. Solaro C, *et al.* An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. *Neurology* 1998; **51:** 609–11.
4. Dunevsky A, Perel AB. Gabapentin for relief of spasticity associated with multiple sclerosis. *Am J Phys Med Rehabil* 1998; **77:** 451–4.
5. Cutter NC, *et al.* Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. *Arch Phys Med Rehabil* 2000; **81:** 164–9.
6. Solaro C, *et al.* Gabapentin is effective in treating nocturnal painful spasms in multiple sclerosis. *Multiple Sclerosis* 2000; **6:** 192–3.
7. Shery T, *et al.* The effects of gabapentin and memantine in acquired and congenital nystagmus: a retrospective study. *Br J Ophthalmol* 2006; **90:** 839–43.

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p.2). Although carbamazepine appears to be the usual choice, gabapentin is also given in the treatment of neuropathic pain,[1-3] including central pain[4] (see p.6), complex regional pain syndrome (see p.6), postherpetic neuralgia[5-7] (see p.9), trigeminal neuralgia (see p.9), and painful diabetic neuropathy[8,9] (see p.6).

1. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. *Anaesthesia* 2002; **57:** 451–62.
2. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther* 2003; **25:** 81–104.
3. Wiffen PJ, *et al.* Gabapentin for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 09/06/08).
4. Schachter SC, Sauter MK. Treatment of central pain with gabapentin: case reports. *J Epilepsy* 1996; **9:** 223–5.
5. Rowbotham M, *et al.* Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* 1998; **280:** 1837–42.
6. Rice ASC, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* 2001; **94:** 215–24.
7. Singh D, Kennedy DH. The use of gabapentin for the treatment of postherpetic neuralgia. *Clin Ther* 2003; **25:** 852–89.
8. Backonja M, *et al.* Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 1998; **280:** 1831–6.
9. Morello CM, *et al.* Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med* 1999; **159:** 1931–7.

Parkinsonism. While some overall ratings of Parkinson's disease (p.791) appeared to be improved by gabapentin in a double-blind study involving 19 patients with advanced parkinsonism, improvements in individual signs and symptoms were not significant.[1] It was also reported that 5 of 6 other patients with progressive supranuclear palsy had experienced worsening of their disease when given gabapentin. Another study[2] in 15 patients with motor complications failed to find any clinically significant benefit from gabapentin therapy.

1. Olson WL, *et al.* Gabapentin for parkinsonism: a double-blind, placebo-controlled, crossover trial. *Am J Med* 1997; **102:** 60–6.
2. Van Blercom N, *et al.* Effects of gabapentin on the motor response to levodopa: a double-blind, placebo-controlled, crossover study in patients with complicated Parkinson disease. *Clin Neuropharmacol* 2004; **27:** 124–8.

Postoperative pain. There is growing interest in the use of analgesic adjuvants including antiepileptics such as gabapentin to modulate opioid dosage and efficacy for postoperative pain (see p.4).[1] A systematic review considered that evidence of benefit for gabapentin in acute pain was lacking, and noted that more effective analgesics for this indication were available.[2] However, a later systematic review found that perioperative use of gabapentin effectively reduced opioid consumption and postoperative pain; further studies were considered warranted.[3] It has been suggested that perioperative use of gabapentin may have other benefits, including pre-operative anxiolysis, attenuation of the haemodynamic response to intubation, and reduction in postoperative nausea and vomiting.[4]

1. Dahl JB, *et al.* 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; **48:** 1130–6.
2. Wiffen PJ, *et al.* Gabapentin for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 09/06/08).
3. Tiippana EM, *et al.* Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007; **104:** 1545–56.
4. Kong VKF, Irwin MG. Gabapentin: a multimodal perioperative drug? *Br J Anaesth* 2007; **99:** 775–86.

Psychiatric disorders. Gabapentin has psychotropic properties and has been tried in the management of several psychiatric disorders, including as an adjunct in the treatment of resistant *depression*[1] (p.373) and in the treatment of *post-traumatic stress disorder*[2] (p.953). Although early open studies[3] found that gabapentin may be of benefit in patients with *bipolar disorder* (p.372) randomised controlled trials have so far failed to confirm this effect.[4-6] Gabapentin is under investigation for the treatment of *social anxiety disorder* (see under Phobic Disorders, p.953).

1. Yasmin S, *et al.* Adjunctive gabapentin in treatment-resistant depression: a retrospective chart review. *J Affect Disord* 2001; **63:** 243–7.
2. Malek-Ahmadi P. Gabapentin and posttraumatic stress disorder. *Ann Pharmacother* 2003; **37:** 664–6.
3. Maidment ID. Gabapentin treatment for bipolar disorders. *Ann Pharmacother* 2001; **35:** 1264–9.
4. Pande AC, *et al.* Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Bipolar Disord* 2000; **2:** 249–55.
5. Frye MA, *et al.* A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 2000; **20:** 607–14.
6. Vieta E, *et al.* A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. *J Clin Psychiatry* 2006; **67:** 473–7.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p.958) is obscure and treatment has been largely empirical. Two small randomised double-blind crossover studies[1,2] found 6 weeks of treatment with gabapentin to produce improvement in symptoms; in patients undergoing haemodialysis the effects were seen with a dose of 300 mg after each of the 3 dialysis sessions per week,[1] although in patients with idiopathic disease the mean effective dose was 1.855 g daily.[2]

A prodrug of gabapentin, gabapentin enacarbil, is reported to be under investigation for the treatment of restless legs syndrome.

1. Thorp ML, *et al.* A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *Am J Kidney Dis* 2001; **38:** 104–8.
2. Garcia-Borreguero D, *et al.* Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology* 2002; **59:** 1573–9.

Soft-tissue rheumatism. Gabapentin may be of benefit in some patients with fibromyalgia (p.13). In a randomised controlled study treatment with oral gabapentin 1.2 to 2.4 g daily in 75 patients produced a greater improvement in mean pain score over 12 weeks than placebo in 75 controls.[1] Sleep problems were also improved, but there was no difference between the groups in a depression rating scale. The drug was generally well tolerated.

1. Arnold LM, *et al.* Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum* 2007; **56:** 1336–44.

Stiff-man syndrome. Gabapentin may improve the symptoms of stiff-man syndrome (see under Muscle Spasm in Uses of Diazepam, p.993) in patients unable to tolerate benzodiazepine therapy.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p.1231); however, gabapentin has also been tried with some success.[1-3]

1. Gironell A, *et al.* A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. *Arch Neurol* 1999; **56:** 475–80.
2. Ondo W, *et al.* Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial. *Mov Disord* 2000; **15:** 678–82.
3. Faulkner MA, *et al.* Gabapentin for the treatment of tremor. *Ann Pharmacother* 2003; **37:** 282–6.

Preparations

USP 31: Gabapentin Capsules; Gabapentin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Abaglin; Alidial; Logistic; Neurontin; Ultraneural; ***Austral.:*** Gabaran; Gantin; Neurontin; Nupentin; Pendine; ***Austria:*** Gabarex; Gabatal; Neurontin; ***Belg.:*** Neurontin; ***Braz.:*** Gabaneurin; Neurontin; Progresse; ***Canad.:*** Neurontin; ***Chile:*** Dineurin; Gabex; Gabictal; Neugabin; Normatol; Ritmenal; ***Cz.:*** Apo-Gab; Gabagamma; Gabalept; Gabanox; Gabator; Gabenta; Neurontin; Nurabax; ***Denm.:*** Neuril; ***Fin.:*** Gabrion; Geabatan†; Neuril; Neurontin; ***Fr.:*** Neurontin; ***Ger.:*** Gabagamma; GabaLich; Gabax; Neurontin; ***Gr.:*** Gabantin; Gabental; Neurontin; Pentin; ***Hong Kong:*** Neurontin; ***Hung.:*** Gordius; Neurontin; ***India:*** Neurontin; ***Indon.:*** Epiven; Gabexal; Ganin; Nepatic; Neurontin; ***Irl.:*** Gabture; Neurontin; Neurostil; ***Israel:*** Neurontin; ***Ital.:*** Neurontin; ***Malaysia:*** Neurontin; ***Mex.:*** Bapex; Gabantin; Gapridol; Neurontin; Nopatic; ***Neth.:*** Neurontin; ***Norw.:*** Neurontin; ***NZ:*** Neurontin; Nupentin; ***Philipp.:*** Neurontin; ***Pol.:*** Gabax; Neurontin; ***Port.:*** Gabamox; Neurontin; ***Rus.:*** Gapentek (Гапентек); Neurontin (Нейронтин); Tebantin (Тебантин); ***S.Afr.:*** Epleptin; Neurontin; ***Singapore:*** Neurontin; ***Spain:*** Equipax†; Gabamerck; Gabatur; Neurontin; Oxaquin; ***Swed.:*** Neurontin; ***Switz.:*** Neurontin; ***Thai.:*** Neurontin; ***Turk.:*** Neurontin; ***UK:*** Neurontin; ***USA:*** Gabarone; Neurontin; ***Venez.:*** Neurontin.

Lacosamide *(USAN, rINN)*

ADD-234037; Erlosamida; Erlosamide; Erlosamidum; Harkoseride; Lacosamida; Lacosamidum; SPM-927. (2*R*)-2-(Acetylamino)-*N*-benzyl-3-methoxypropanamide.

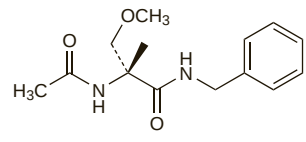
Эрльозамид

$C_{13}H_{18}N_2O_3$ = 250.3.

CAS — 175481-36-4.

ATC — N03AX18.

ATC Vet — QN03AX18.



Profile

Lacosamide is an antiepileptic drug that is under investigation for adjunctive therapy in partial seizures. It is also being studied for use in diabetic neuropathic pain, fibromyalgia, osteoarthritis, and migraine.

◊ References.

1. Doty P, *et al.* Lacosamide. *Neurotherapeutics* 2007; **4:** 145–8.
2. Rauck RL, *et al.* Lacosamide in painful diabetic peripheral neuropathy: a phase 2 double-blind placebo-controlled study. *Clin J Pain* 2007; **23:** 150–8.