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.

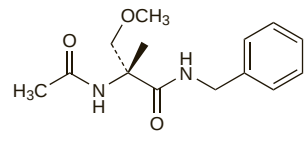
Эрльозамид

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

3. Ben-Menachem E, *et al.* Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007; **48:** 1308–17.
4. Biton V, *et al.* Intravenous lacosamide as replacement for oral lacosamide in patients with partial-onset seizures. *Epilepsia* 2008; **49:** 418–24.
5. Ben-Menachem E. Lacosamide: an investigational drug for adjunctive treatment of partial-onset seizures. *Drugs Today* 2008; **44:** 35–40.

Lamotrigine *(BAN, USAN, rINN)*

BW-430C; Lamotrigiini; Lamotrigin; Lamotrigina; Lamotriginum; Lamotrijin. 6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diyldiamine.

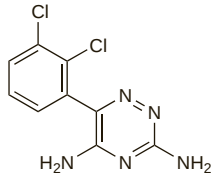
Ламотригин

$C_9H_7Cl_2N_5$ = 256.1.

CAS — 84057-84-1.

ATC — N03AX09.

ATC Vet — QN03AX09.



Adverse Effects and Treatment

Skin rashes may occur during therapy with lamotrigine; severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, especially in children, and usually occur within 8 weeks of starting lamotrigine (see Effects on the Skin, below). Symptoms such as fever, malaise, flu-like symptoms, drowsiness, lymphadenopathy, facial oedema and, rarely, hepatic dysfunction have been reported. Blood dyscrasias such as leucopenia, neutropenia, and thrombocytopenia have also been reported, sometimes with rashes as part of a hypersensitivity syndrome.

Movement disorders such as tics, ataxia, nystagmus, and tremor have occurred; lamotrigine may worsen symptoms in patients with pre-existing Parkinson's disease. Other adverse effects include angioedema, photosensitivity, diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, insomnia, headache, tiredness, nausea and vomiting, irritability and aggression, hallucinations, agitation, and confusion. Very rarely, lupus-like reactions and increases in seizure frequency have been reported.

◊ Licensed product information states that there have been rare instances of death after a rapidly progressive illness involving status epilepticus, multi-organ dysfunction, and disseminated intravascular coagulation in patients taking multiple antiepileptics including lamotrigine, although the role of lamotrigine remains to be established. It has been suggested[1] that multi-organ failure and disseminated intravascular coagulation, with associated rhabdomyolysis, are complications of severe convulsive seizures rather than of lamotrigine therapy. However, there has been a report[2] of a patient with no history of generalised seizures who developed a syndrome of disseminated intravascular coagulation, rhabdomyolysis, renal failure, maculopapular rash, and ataxia 14 days after lamotrigine was added to her antiepileptic regimen. Two cases of disseminated intravascular coagulation were found in a cohort of 11 316 patients involved in prescription-event monitoring of lamotrigine therapy in general practice.[3]

1. Yuen AWC, Bihari DJ. Multiorgan failure and disseminated intravascular coagulation in severe convulsive seizures. *Lancet* 1992; **340:** 618.
2. Schaub JEM, *et al.* Multisystem adverse reaction to lamotrigine. *Lancet* 1994; **344:** 481.
3. Mackay FJ, *et al.* Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; **38:** 881–6.

Effects on the blood. Septic shock secondary to leucopenia occurred in a patient when lamotrigine was added to therapy with sodium valproate.[1] There has also been a report of agranulocytosis in a child started on high-dose lamotrigine monotherapy.[2] The fall in the blood count was noted several days after lamotrigine had been stopped due to skin rash. The UK CSM subsequently reported[3] that 7 cases of aplastic anaemia, 12 of bone-marrow depression, and 20 of pancytopenia associated with lamotrigine had been received worldwide. Given the extensive usage of lamotrigine the CSM considered the risk of aplastic anaemia to be small and routine blood monitoring was not recommended. However, prescribers were warned to be alert for symptoms and signs suggestive of bone-marrow depression.

1. Nicholson RJ, *et al.* Leucopenia associated with lamotrigine. *BMJ* 1995; **310:** 504.
2. de Camargo OAK, Bode H. Agranulocytosis associated with lamotrigine. *BMJ* 1999; **318:** 1179.
3. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal): rare blood dyscrasias. *Current Problems* 2000; **26:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

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

Effects on the liver. Fatal fulminant hepatic failure has been reported[1] in a patient after addition of lamotrigine to antiepileptic therapy with sodium valproate and carbamazepine. Another fatal case was reported[2] in a patient who was given lamotrigine for bipolar disorder; she was also taking other drugs for pain and insomnia. Reversible eosinophilic hepatitis occurred[3] as part of a hypersensitivity syndrome in a patient given lamotrigine for seizures.

1. Makin AJ, *et al.* Fulminant hepatic failure induced by lamotrigine. *BMJ* 1995; **311:** 292.
2. Overstreet K, *et al.* Fatal progressive hepatic necrosis associated with lamotrigine treatment: a case report and literature review. *Dig Dis Sci* 2002; **47:** 1921–5.
3. Fix OK, *et al.* Eosinophilic hepatitis caused by lamotrigine. *Clin Gastroenterol Hepatol* 2006; **4:** xxvi.

Effects on the lungs. Interstitial pneumonitis with pulmonary infiltrates occurred when lamotrigine was added to antiepileptic therapy in a 57-year-old woman; the condition resolved when lamotrigine was stopped.[1]

1. Saravanan N, *et al.* Interstitial pneumonitis during lamotrigine therapy. *Br J Clin Pharmacol* 2005; **60:** 666–7.

Effects on mental function. Acute *psychosis* was reported[1] in 6 out of about 1400 patients when lamotrigine was added to antiepileptic therapy and/or when the dose of lamotrigine was increased. Symptoms resolved when lamotrigine was stopped, and recurred in 1 case of rechallenge.

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

1. Brandt C, *et al.* Development of psychosis in patients with epilepsy treated with lamotrigine: report of six cases and review of the literature. *Epilepsy Behav* 2007; **11:** 133–9.

Effects on the nervous system. Of 93 patients with idiopathic generalised epilepsy who were treated with lamotrigine, 5 adults experienced *de novo* or exacerbated myoclonic jerks.[1] In each case, symptoms resolved when the dose of lamotrigine was reduced by 25 to 50% or stopped altogether. In another report, a 17-year-old girl with idiopathic Rolandic epilepsy experienced a sudden increase in seizure frequency when lamotrigine was added to therapy with sodium valproate; other adverse effects included emotional lability, headaches, and drowsiness.[2] Again symptoms resolved when lamotrigine was stopped.[2]

Overdose of lamotrigine has been known to cause seizures (see below).

1. Crespel A, *et al.* Lamotrigine associated with exacerbation or de novo myoclonus in idiopathic generalized epilepsies. *Neurology* 2005; **65:** 762–4.
2. Cerminara C, *et al.* Lamotrigine-induced seizure aggravation and negative myoclonus in idiopathic rolandic epilepsy. *Neurology* 2004; **63:** 373–5.

Effects on the skin. Rashes account for withdrawal from therapy in about 2% of those given lamotrigine,[1,2] and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis occur in about 1 in 1000 adult patients.[3,4] The majority of rashes resolve once lamotrigine has been stopped; however, some patients have developed permanent scarring and there have been rare reports of fatalities. The main risk factors appear to be use with valproate, exceeding the recommended initial dose of lamotrigine or the recommended rate of dose escalation, and a history of antiepileptic-induced rash. The risk appears to be greater in children[1,4-6] and has been estimated to be between 1 in 300 and 1 in 50. These skin reactions usually occur within 8 weeks of starting therapy with lamotrigine, but onset as early as the first day and as late as 2 years has been noted.[7] After continuing reports of serious skin reactions in children, UK recommended dosage regimens for children have been revised to further reduce the risk of such reactions.[8] For the relative incidence of rash with different antiepileptics see under Phenytoin, p.496.

1. Mackay FJ, *et al.* Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; **38:** 881–6.
2. Messenheimer J, *et al.* Safety review of adult clinical trial experience with lamotrigine. *Drug Safety* 1998; **18:** 281–96.
3. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal) and serious skin reactions. *Current Problems* 1996; **22:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015622&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
4. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal): increased risk of serious skin reactions in children. *Current Problems* 1997; **23:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
5. Mitchell P. Paediatric lamotrigine use hit by rash reports. *Lancet* 1997; **349:** 1080.
6. Hirsch LJ, *et al.* Predictors of lamotrigine-associated rash. *Epilepsia* 2006; **47:** 318–22.
7. Adverse Drug Reactions Advisory Committee (ADRAC). Lamotrigine and severe skin reactions. *Aust Adverse Drug React Bull* 1997; **16:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr9702.htm (accessed 09/06/08)
8. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal): revised doses for children. *Current Problems* 2000; **26:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Overdosage. An evaluation[1] of 493 cases of lamotrigine-only overdoses reported to the American Association of Poison Control Centers over a 2-year period found that 52.1% of patients had no toxic effects. The most commonly reported adverse effects were drowsiness, nausea, vomiting, and ataxia. Serious effects such as seizures, coma, and respiratory depression were reported in 0.6 to 1.2% of cases; no deaths were reported.

No serious toxicity was seen in a patient who deliberately took an overdose of 1.35 g of lamotrigine and was subsequently treated with gastric lavage and activated charcoal.[2] Symptoms at presentation one hour after ingestion had included nystagmus and muscle hypertonicity. ECG monitoring had revealed widening of the QRS interval. Low-grade fever, erythema, and periorbital oedema suggestive of a hypersensitivity syndrome developed in another patient who inadvertently received lamotrigine 2.7 g daily for 4 days.[3] The patient recovered after corticosteroid treatment and stopping lamotrigine. Generalised tonic-clonic seizures, tremor, muscle weakness, ataxia, and hypertonia were reported[4] in a 2-year-old child after ingestion of 800 mg of lamotrigine. Symptoms resolved within 24 hours after treatment with gastric lavage and activated charcoal, midazolam, and fluids. Plasma-lamotrigine concentrations were in the high adult therapeutic range (3.8 micrograms/mL) with a slow elimination rate. Generalised seizures also occurred[5] after an unknown quantity of lamotrigine was ingested by a 19-month-old child who had no history of seizures; other presenting symptoms included tachycardia and vomiting. The serum-lamotrigine concentration measured 1 hour post ingestion was 20.3 mg/L. Symptoms resolved within 24 hours after treatment with trimethobenzamide and activated charcoal.

For a further review of the features and management of poisoning with some antiepileptics, including lamotrigine, see under Phenytoin, p.497.

1. Lofton AL, Klein-Schwartz W. Evaluation of lamotrigine toxicity reported to poison centers. *Ann Pharmacother* 2004; **38:** 1811–15.
2. Buckley NA, *et al.* Self-poisoning with lamotrigine. *Lancet* 1993; **342:** 1552–3.
3. Mylonakis E, *et al.* Lamotrigine overdose presenting as anticonvulsant hypersensitivity syndrome. *Ann Pharmacother* 1999; **33:** 557–9.
4. Briassoulis G, *et al.* Lamotrigine childhood overdose. *Pediatr Neurol* 1998; **19:** 239–42.
5. Thundiyil JG, *et al.* Lamotrigine-induced seizures in a child: case report and literature review. *Clin Toxicol* 2007; **45:** 169–72.

Precautions

Lamotrigine should be given with caution to patients with hepatic or renal impairment. All patients should be warned to see their doctor immediately if rashes or symptoms associated with hypersensitivity develop. To minimise the risk of developing serious skin reactions, dosage recommendations should not be exceeded. Particular care is needed in patients also receiving valproate—see Interactions, below.

Withdrawal of lamotrigine should be considered if rash, fever, flu-like symptoms, drowsiness, or worsening of seizure control occurs. Care is required when withdrawing lamotrigine therapy—see also under Uses and Administration, below. Abrupt withdrawal should be avoided unless serious skin reactions have occurred. Lamotrigine should not be restarted in patients with previous hypersensitivity.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of lamotrigine by mothers during breast feeding may be of concern, since there is the potential for therapeutic serum concentrations to occur in the infant. A report in 4 breast-fed infants whose mothers were taking lamotrigine found that although serum concentrations of the drug 10 days after birth were about 30% of maternal concentrations in 3 infants, no short-term adverse effects were seen; the drug was undetectable in the fourth.[2] A study[3] in 6 mothers taking lamotrigine found that the relative dose in their breast-fed infants was 7.6% (mean absolute dose: 450 micrograms/kg daily) and infant plasma concentrations were 18% of maternal concentrations; no adverse effects were reported. The authors also noted that no adverse effects were reported in 12 previous cases.