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.

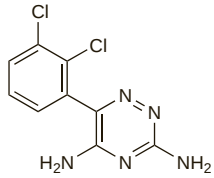
Ламотригин

$C_9H_7Cl_2N_5$ = 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.

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


1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)
2. Liporace J, *et al.* Concerns regarding lamotrigine and breastfeeding. *Epilepsy Behav* 2004; **5:** 102–5.
3. Page-Sharp M, *et al.* Transfer of lamotrigine into breast milk. *Ann Pharmacother* 2006; **40:** 1470–1.


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

**Hepatic impairment.** The pharmacokinetics of lamotrigine were not significantly altered in patients with moderate cirrhosis;[1] however, those with severe cirrhosis showed significantly lower oral clearance and longer elimination half-lives than those in healthy subjects.

The recommended licensed doses in patients with hepatic impairment are given under Uses and Administration, below.


1. Marcellin P, *et al.* Influence of cirrhosis on lamotrigine pharmacokinetics. *Br J Clin Pharmacol* 2001; **51:** 410–14.


**Intellectual impairment.** Aggressive behaviour has been reported in intellectually impaired patients given lamotrigine.[1] Of 19 such patients given lamotrigine, aggressive behaviour developed in 9; the drug was stopped in 5, and stopped but reintroduced in a further 2, together with psychiatric management. One patient responded to a reduction in lamotrigine dosage.


1. Beran RG, Gibson RJ. Aggressive behaviour in intellectually challenged patients with epilepsy treated with lamotrigine. *Epilepsia* 1998; **39:** 280–2.


**Pregnancy.** For comments on the management of epilepsy during pregnancy, see p.468. For reference to alteration of lamotrigine pharmacokinetics in pregnancy, see under Pharmacokinetics, below.

There is a theoretical risk of teratogenicity with lamotrigine because, like valproate, it is a folate antagonist. In 2002 the manufacturer of lamotrigine, *GlaxoSmithKline*, reported[1] that it had follow-up information on 395 outcomes of pregnancies exposed to lamotrigine between September 1992 and September 2001 from the International Lamotrigine Pregnancy Registry. Major birth defects were found in 13 infants but no distinctive pattern of abnormalities suggestive of a common cause could be identified. Of the 168 who had been exposed to lamotrigine monotherapy during the first trimester, birth defects were reported in 3 (1.8%). The frequency of major birth defects in pregnancies exposed to polytherapy containing lamotrigine with valproate was 10% compared with 4.3% in lamotrigine polytherapy without valproate. Although it was considered that the sample sizes were too small to rule out a small increase in the frequency of major birth defects, it was noted that the frequency of malformations after lamotrigine monotherapy did not differ from that reported in the literature for women with epilepsy receiving antiepileptic monotherapy. Updated results from 785 pregnancies up to March 2004 included 414 first-trimester exposures to lamotrigine monotherapy, of which 12 were associated with a major abnormality.[2] As of March 2006, the registry had recorded 802 first-trimester exposures to lamotrigine monotherapy with major abnormalities occurring in 22; there was no evidence to suggest a dose-response relationship with daily doses of up to 400 mg.[3]

In August 2006, the manufacturer[4] reported that data from the North American Antiepileptic Drug Pregnancy Registry suggested an association between lamotrigine and an increased risk of oral clefts. Of 564 first-trimester exposures to lamotrigine monotherapy, 5 cases of oral clefts were reported giving an incidence rate of 8.9 per 1000 compared with 0.37 per 1000 in the reference population. Again, however, no increase in the overall risk of major malformations was found. Analysis of data from other pregnancy registries found 4 additional cases of oral clefts in about 2200 first-trimester exposures to lamotrigine monotherapy.


1. Tennis P, Eldridge RR. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Preliminary results on pregnancy outcomes in women using lamotrigine. *Epilepsia* 2002; **43:** 1161–7.
2. Cunnington M, Tennis P. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. *Neurology* 2005; **64:** 955–60.
3. Cunnington M, *et al.* International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. *Epilepsia* 2007; **48:** 1207–10.
4. GlaxoSmithKline, Canada. Association of Lamictal® (lamotrigine) with an increased risk of non-syndromic oral clefts (issued 1st August, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_2_hpc-cps-eng.pdf (accessed 01/09/08)


**Renal impairment.** Results from a pharmacokinetic study[1] indicated that impaired renal function was likely to have little effect on plasma concentrations of lamotrigine. The drug is mainly cleared by metabolism and although the glucuronide metabolite accumulates it is inactive. Nevertheless, there is limited clinical experience with lamotrigine in such patients and caution was recommended.


1. Wootton R, *et al.* Comparison of the pharmacokinetics of lamotrigine in patients with chronic renal failure and healthy volunteers. *Br J Clin Pharmacol* 1997; **43:** 23–7.


## 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. The metabolism of lamotrigine is enhanced by the enzyme inducers carbamazepine, phenytoin, phenobarbital, and primidone, and inhibited by valproate (see below).

**Analgesics.** *Paracetamol* affects the metabolic disposition of lamotrigine but the clinical significance of this interaction remains to be determined.[1] Paracetamol reduced the area under the plasma concentration-time curve for lamotrigine, reduced lamotrigine's half-life, and increased the percentage of lamotrigine recovered in the urine.


1. Depot M, *et al.* Kinetic effects of multiple oral doses of acetaminophen on a single oral dose of lamotrigine. *Clin Pharmacol Ther* 1990; **48:** 346–55.


**Antibacterials.** Use with *rifampicin* significantly increased the clearance of lamotrigine.[1] The total urinary excretion of lamotrigine and the amount excreted as glucuronide were significantly higher compared with placebo.


1. Ebert U, *et al.* Effects of rifampicin and cimetidine on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects. *Eur J Clin Pharmacol* 2000; **56:** 299–304.


**Antidepressants.** An epileptic patient maintained on lamotrigine 200 mg daily complained[1] of increasing confusion and cognitive impairment after starting *sertraline* 25 mg daily for post-traumatic disorder; after 6 weeks her lamotrigine blood concentrations had risen from 2.5 to 5.1 micrograms/mL during this period. The adverse effects cleared and blood concentrations of lamotrigine fell to 3.1 micrograms/mL within 3 weeks of changing the daily dosage to lamotrigine 100 mg and sertraline 50 mg. A patient, with poorly controlled epilepsy, who initially had been taking lamotrigine 450 mg and sertraline 75 mg together daily for 6 weeks without adverse effects had marked sedation, fatigue, and decreased cognition 6 weeks after the daily dosage of lamotrigine was increased to 600 mg. Her lamotrigine blood concentration was 19.3 micrograms/mL. The patient was subsequently stabilised on lamotrigine 800 mg and sertraline 50 mg daily and had less sedation and fatigue and clearer cognition; blood concentrations of lamotrigine fell to 9.8 micrograms/mL.


1. Kaufman KR, Gerner R. Lamotrigine toxicity secondary to sertraline. *Seizure* 1998; **7:** 163–5.


**Antiepileptics.** *Valproate* can inhibit the metabolism of lamotrigine resulting in increased concentrations of lamotrigine. This effect can be beneficial in the control of certain seizures, although careful monitoring is required as toxicity may occur. Disabling tremor occurred in 3 patients taking such a combination which resolved when the dose of lamotrigine or valproate was reduced.[1] Other reports of toxicity, resolving on reduction of the lamotrigine dose, were marked by sedation, ataxia, and fatigue,[2] or delirium.[3] Symptoms of neurotoxicity were reported in 3 patients on lamotrigine therapy who were given valproate, intravenously then orally, for absence status epilepticus. Serum concentrations of lamotrigine in these patients were raised about three- to sevenfold.[4] Reversible encephalopathy has been reported[5] when sodium valproate was substituted for phenytoin in a patient also taking lamotrigine, although her clinical condition had been satisfactory on this new regimen for several months. Symptoms improved when the doses of both valproate and lamotrigine were reduced. Pharmacokinetic studies[6,7] in healthy adults have attempted to elucidate the mechanism of the interaction between lamotrigine and valproate. The clearance of lamotrigine was found to be reduced, and exposure and elimination half-life increased when valproate was also given. Renal elimination was not affected and the investigators[6] suggested that there was hepatic competition for glucuronidation between valproate and lamotrigine. However, there was no substantial alteration in the linear kinetics of lamotrigine in the presence of therapeutic plasma concentrations of valproate.[7] Similar observations were made when lamotrigine was added to existing antiepileptic regimens in children,[8] although the clinical relevance of the influence of age on the pharmacokinetics remains to be determined. Both young age and use with valproate are risk factors for lamotrigine-induced dermatological toxicity—see Effects on the Skin, above.

For details of dosage reductions required for lamotrigine used with valproate, see Uses and Administration, below.

Other antiepileptics also affect plasma concentrations of lamotrigine. In contrast to valproate, *carbamazepine*, *phenytoin*, or *phenobarbital* all markedly induced the elimination of lamotrigine.[9] Others have confirmed a reduction in plasma-lamotrigine concentrations when given with phenytoin and other enzyme-inducing antiepileptics,[10] but analysis of results from another study[11] suggested that the increase in lamotrigine clearance by phenytoin and carbamazepine was of minimal clinical significance. *Oxcarbazepine* has also been reported[12] to decrease serum-lamotrigine concentrations (although to a lesser extent than carbamazepine). However, a study[13] in healthy subjects found that oxcarbazepine did not affect the pharmacokinetics of lamotrigine, although adverse effects occurred more frequently when they were used together (for a report of severe toxicity associated with such use see p.491). *Mesuximide* was found[12,14] to have a marked inducing effect on the metabolism of lamotrigine. In one study,[14] plasma-lamotrigine concentrations were significantly reduced when given together.

For reports of an interaction between lamotrigine and carbamazepine, see p.474. For the effect of lamotrigine on clonazepam concentrations, see p.990.


1. Reutens DC, *et al.* Disabling tremor after lamotrigine with sodium valproate. *Lancet* 1993; **342:** 185–6.
2. Pisani F, *et al.* Interaction of lamotrigine with sodium valproate. *Lancet* 1993; **341:** 1224.
3. Mueller TH, Beeber AR. Delirium from valproic acid with lamotrigine. *Am J Psychiatry* 2004; **161:** 1128–9.
4. Burneo JG, *et al.* Neurotoxicity following addition of intravenous valproate to lamotrigine therapy. *Neurology* 2003; **60:** 1991–2.
5. Hennessy MJ, Wiles CM. Lamotrigine encephalopathy. *Lancet* 1996; **347:** 974–5.
6. Yuen AWC, *et al.* Sodium valproate acutely inhibits lamotrigine metabolism. *Br J Clin Pharmacol* 1992; **33:** 511–13.
7. Anderson GD, *et al.* Bidirectional interaction of valproate and lamotrigine in healthy subjects. *Clin Pharmacol Ther* 1996; **60:** 145–56.
8. Vauzelle-Kervroëdan F, *et al.* Influence of concurrent antiepileptic medication on the pharmacokinetics of lamotrigine as add-on therapy in epileptic children. *Br J Clin Pharmacol* 1996; **41:** 325–30.
9. May TW, *et al.* Serum concentrations of lamotrigine in epileptic patients: the influence of dose and comedication. *Ther Drug Monit* 1996; **18:** 523–31.
10. Battino D, *et al.* Lamotrigine plasma concentrations in children and adults: influence of age and associated therapy. *Ther Drug Monit* 1997; **19:** 620–7.
11. Grasela TH, *et al.* Population pharmacokinetics of lamotrigine adjunctive therapy in adults with epilepsy. *J Clin Pharmacol* 1999; **39:** 373–84.
12. May TW, *et al.* Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in epileptic patients with and without valproic acid comedication: results of a retrospective study. *Ther Drug Monit* 1999; **21:** 175–81.
13. Theis JGW, *et al.* Lack of pharmacokinetic interaction between oxcarbazepine and lamotrigine. *Neuropsychopharmacology* 2005; **30:** 2269–74.
14. Besag FM, *et al.* Methsuximide lowers lamotrigine blood levels: a pharmacokinetic antiepileptic drug interaction. *Epilepsia* 2000; **41:** 624–7.


**Antipsychotics.** An apparent interaction between lamotrigine and *aripiprazole*, resulting in Stevens-Johnson syndrome, has been reported[1] in 2 patients with schizophrenia after the introduction of lamotrigine; both patients recovered with supportive treatment.


1. Shen Y-C, *et al.* Concomitant use of lamotrigine and aripiprazole increases risk of Stevens-Johnson syndrome? *Int Clin Psychopharmacol* 2007; **22:** 247–8.


**Antivirals.** A study[1] in healthy subjects found that ritonavir-boosted lopinavir decreased the steady-state minimum plasma concentration of lamotrigine by about 55%; doubling the dose of lamotrigine achieved concentrations similar to those with lamotrigine alone.


1. van der Lee MJ, *et al.* Lopinavir/ritonavir reduces lamotrigine plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2006; **80:** 159–68.


**Sex hormones.** Studies in patients taking lamotrigine have indicated that *combined oral contraceptives*[1,2] may halve plasma concentrations of the antiepileptic. Other studies[3,4] have also found a significant increase in lamotrigine-plasma concentrations within one week of stopping contraceptive therapy; however, wide interpatient variability was noted in one study.[3] Significant adjustments in maintenance doses of lamotrigine may be needed if combined contraceptives are started or stopped (see below), and patients should be warned not to make changes in their contraceptive therapy without consulting their physician.[5] However, in a study,[6] progestogen-only contraceptives did not appear to affect lamotrigine concentrations. Licensed drug information recommends that, when starting treatment with combined oral contraceptives, the dose of lamotrigine may need to be increased by as much as twofold in those women not taking drugs known to induce cytochrome P450-mediated metabolism of lamotrigine; conversely, the dose of lamotrigine may need to be halved when stopping contraceptive therapy in women not taking enzyme inducers. Dosage adjustment may not be necessary when starting or stopping combined oral contraceptive therapy in women taking lamotrigine with known enzyme inducers.

Adjustments may also be needed if other hormonal preparations are taken with lamotrigine.

Some reduction in plasma concentrations of levonorgestrel, and to a lesser extent ethinylestradiol, may also occur with lamotrigine, and there have been reports of breakthrough bleeding and unexpected pregnancies.[5]


1. Sabers A, *et al.* Oral contraceptives reduce lamotrigine plasma levels. *Neurology* 2003; **61:** 570–1.
2. Sidhu J, *et al.* The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* 2006; **61:** 191–9.

3. Contin M, *et al.* Variation in lamotrigine plasma concentrations with hormonal contraceptive monthly cycles in patients with epilepsy. *Epilepsia* 2006; **47:** 1573–5.
4. Christensen J, *et al.* Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial *Epilepsia* 2007; **48:** 484–9.
5. GlaxoSmithKline, Canada. Important new safety information concerning the antiepileptic, Lamictal (lamotrigine) (issued September 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_hpc-cps-eng.pdf (accessed 01/09/08)
6. Reimers A, *et al.* Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia* 2005; **46:** 1414–17.

## Pharmacokinetics

Lamotrigine is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of 98%. Peak plasma concentrations occur about 2.5 hours after oral doses. It is widely distributed in the body and is reported to be about 55% bound to plasma proteins. It is extensively metabolised in the liver and excreted almost entirely in urine, principally as an inactive glucuronide conjugate. It slightly induces its own metabolism and the mean elimination half-life is reported to be 24 to 35 hours. Clearance is reported to be higher in children aged up to 12 years than in adults, with the highest values occurring in those under 5 years of age. Lamotrigine is distributed into breast milk.

The pharmacokinetics of lamotrigine are affected by other antiepileptics (see Interactions, above).

◊ General references.

1. Rambeck B, Wolf P. Lamotrigine clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 433–43.
2. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
3. Reimers A, *et al.* Lamotrigine in children and adolescents: the impact of age on its serum concentrations and on the extent of drug interactions. *Eur J Clin Pharmacol* 2007; **63:** 687–92.
4. Punyawudho B, *et al.* Population pharmacokinetics of lamotrigine in elderly patients. *J Clin Pharmacol* 2008; **48:** 455–63.

**Hepatic impairment.** See under Precautions, above.

**Pregnancy.** Decreased plasma-lamotrigine concentrations have occurred during pregnancy, with deterioration of seizure control and a need for dosage adjustment in some patients.

References

1. Pennell PB, *et al.* The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* 2004; **62:** 292–5.
2. de Haan G-J, *et al.* Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 2004; **63:** 571–3.
3. Petrenaite V, *et al.* Individual changes in lamotrigine plasma concentrations during pregnancy. *Epilepsy Res* 2005; **65:** 185–8.

**Renal impairment.** See under Precautions, above.

**Therapeutic drug monitoring.** A literature review[1] concluded that a clear relationship between lamotrigine concentrations and toxicity or antiepileptic efficacy has not been demonstrated. Routine therapeutic drug monitoring was therefore not recommended and clinical end-points rather than plasma concentrations remained the best guide for dosage adjustment of lamotrigine.

1. Chong E, Dupuis LL. Therapeutic drug monitoring of lamotrigine. *Ann Pharmacother* 2002; **36:** 917–20.

## Uses and Administration

Lamotrigine, a phenyltriazine compound, is an antiepileptic used mainly for monotherapy or adjunctive treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures. It may be used for seizures associated with the Lennox-Gastaut syndrome and for the maintenance treatment of bipolar disorder.

The doses given below for the use of lamotrigine in **epilepsy** are those licensed in the UK; similar doses are given in the USA although the use of lamotrigine is more limited than in the UK.

- The initial oral dose for use as *monotherapy* is 25 mg once daily for 2 weeks followed by 50 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 50 to 100 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily, given as a single dose or in 2 divided doses. Some patients have required up to 500 mg daily
- The initial oral dose of lamotrigine for use as an *adjunct* to therapy with enzyme-inducing antiepileptics (but *not with valproate*) is 50 mg once daily for 2 weeks followed by 50 mg twice daily for 2 weeks; thereafter the dose is increased by a maximum of 100 mg every 1 to 2 weeks to usual maintenance doses of 200 to 400 mg daily given in 2 divided doses. Some patients have required up to 700 mg daily
- In those *taking valproate* the initial oral dose of lamotrigine is 25 mg every other day for 2 weeks followed by 25 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 25 to 50 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily given as a single dose or in 2 divided doses
- In those *taking oxcarbazepine* but no enzyme-inducing or -inhibiting antiepileptics the dosage regimen of adjunctive lamotrigine is as for monotherapy

If the potential for interaction with adjunctive antiepileptics is unknown, treatment with lamotrigine should be started with lower doses such as those used with valproate. For comment on the need to modify maintenance doses when starting or stopping oral contraceptives see Sex Hormones, under Interactions, above.

For doses in children, see below.

In the management of **bipolar disorder**, the target dose of lamotrigine is 200 mg daily as *monotherapy*; for patients *taking valproate* the target dose is 100 mg daily and in those taking enzyme-inducing drugs (but *not with valproate*) the target dose is 400 mg daily. Lamotrigine should be started at a reduced dose and increased gradually to the target dose in a regimen similar to that used in the treatment of epilepsy (see above).

Doses should be reduced in patients with hepatic impairment regardless of indication (see below).

As with other antiepileptics, withdrawal of lamotrigine 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. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465. Licensed drug information recommends that regardless of indication the withdrawal of lamotrigine should be tapered over at least 2 weeks.

**Administration in children.** Lamotrigine is used as an adjunct in the treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures in children aged 2 years and over; it is used as monotherapy in those over 12 years of age. Lamotrigine may also be used for seizures associated with the Lennox-Gastaut syndrome.

The doses given below are those licensed in the UK; similar doses are given in the USA although the use of lamotrigine is more limited than in the UK.

- In those taking enzyme-inducing antiepileptics (but *not with valproate*) the initial oral dose of lamotrigine is 600 micrograms/kg daily in 2 divided doses for 2 weeks followed by 1.2 mg/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 1.2 mg/kg every 1 to 2 weeks to usual maintenance doses of 5 to 15 mg/kg daily given in 2 divided doses
- In those *taking valproate* the initial oral dose of lamotrigine is 150 micrograms/kg once daily for 2 weeks followed by 300 micrograms/kg once daily for 2 weeks; thereafter the dose is increased by a maximum of 300 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 5 mg/kg daily, given as a single dose or in 2 divided doses
- In those taking *oxcarbazepine* but no enzyme-inducing or -inhibiting antiepileptics the initial oral dose of lamotrigine, given as a single dose or in 2 divided doses, is 300 micrograms/kg daily for 2 weeks, followed by 600 micrograms/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 600 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 10 mg/kg daily, to a maximum of 200 mg daily.

If the calculated daily dose of lamotrigine lies between 1 and 2 mg, then 2 mg may be given on alternate days for the first 2 weeks of therapy. Lamotrigine should not be given if the calculated daily dose is less than 1 mg.

Children over 12 years of age may be given the adult dosage regimen for monotherapy and adjunctive therapy (see above).

**Administration in hepatic impairment.** UK licensed product information for lamotrigine recommends that doses should be reduced by about 50% in patients with moderate hepatic impairment (Child-Pugh category B), and by about 75% in severe impairment (Child-Pugh category C). US licensed product information recommends that doses should be reduced by about 25% in patients with moderate to severe hepatic impairment without ascites, and by about 50% in those with severe hepatic impairment with ascites.

**Anxiety disorders.** Small studies have suggested that lamotrigine may relieve some of the symptoms of post-traumatic stress disorder (p.953).

References.

1. Hertzberg MA, *et al.* A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry* 1999; **45:** 1226–9.
2. Hageman I, *et al.* Post-traumatic stress disorder: a review of psychobiology and pharmacotherapy. *Acta Psychiatr Scand* 2001; **104:** 411–22.

**Bipolar disorder.** In a multicentre placebo-controlled study involving 195 patients, lamotrigine 50 or 200 mg daily by mouth produced dose-related improvement in patients with bipolar disorder (p.372) experiencing a major depressive episode.[1] Further data from randomised controlled studies[2-8] have confirmed benefit for depressive symptoms (although not for mania), and reviews[9-13] have generally favoured its use, although some have queried the strength of the evidence.[14] Guidelines for the treatment of bipolar disorder now recommend lamotrigine as a first-line option for bipolar depression, and it is licensed for such use in a number of countries (see also Uses and Administration, above).

1. Calabrese JR, *et al.* A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psychiatry* 1999; **60:** 79–88.
2. Bowden CL, *et al.* Lamotrigine in the treatment of bipolar depression. *Eur Neuropsychopharmacol* 1999; **9** (suppl 4): S113–S117.
3. Calabrese JR, *et al.* A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. *J Clin Psychiatry* 2000; **61:** 841–50.
4. Ichim L, *et al.* Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann Clin Psychiatry* 2000; **12:** 5–10.
5. Obrocea GV, *et al.* Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry* 2002; **51:** 253–60.
6. Bowden CL, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 2003; **60:** 392–400. Correction. *ibid.* 2004; **61:** 680.
7. Calabrese JR, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003; **64:** 1013–24.
8. Nierenberg AA, *et al.* Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry* 2006; **163:** 210–16.
9. Engle PM, Heck AM. Lamotrigine for the treatment of bipolar disorder. *Ann Pharmacother* 2000; **34:** 258–62.
10. Hurley SC. Lamotrigine update and its use in mood disorders. *Ann Pharmacother* 2002; **36:** 860–73.
11. Goldsmith DR, *et al.* Lamotrigine: a review of its use in bipolar disorder. *Drugs* 2003; **63:** 2029–50.
12. Muzina DJ, *et al.* Lamotrigine and antiepileptic drugs as mood stabilizers in bipolar disorder. *Acta Psychiatr Scand Suppl* 2005; 21–8.
13. Smith LA, *et al.* Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disord* 2007; **9:** 394–412.
14. van der Loos MLM, *et al.* Lamotrigine bij de behandeling van bipolaire stoornissen: een overzicht. *Tijdschr Psychiatr* 2007; **49:** 95–103.

**Epilepsy.** Lamotrigine is used in the treatment of epilepsy (p.465). It is used in partial seizures with or without secondary generalisation, and in generalised tonic-clonic seizures, although valproate is the drug of choice in the latter where these are associated with the syndrome of primary generalised epilepsy. It is also recommended in absence seizures, although the evidence base is not particularly strong, and may be used in juvenile myoclonic epilepsy and tried in tonic or atonic seizures.

As monotherapy for partial seizures with or without secondary generalisation, lamotrigine was found to be better than carbamazepine (the established first-line drug) in terms of time to treatment failure and tolerability.[1] In patients with newly-diagnosed partial seizures with or without secondary generalisation, lamotrigine had a similar efficacy to carbamazepine, but again was better tolerated.[2] A systematic review[3] of randomised, placebo-controlled studies concluded that lamotrigine is also effective in reducing the seizure frequency when added to current antiepileptic regimens in patients with refractory partial seizures.

As monotherapy for primary generalised and unclassifiable seizures lamotrigine was found[4] to be significantly inferior to valproate (the established first-line drug) in terms of seizure control, with almost twice the failure rate; valproate was also significantly more effective for achieving 12-month remission and prolonging the time to first seizure. Benefit was seen with adjunctive lamotrigine when compared with placebo in children[5] and adults[6] for treatment-resistant primary generalised seizures; it was also suggested[6] that lamotrigine therapy may be appropriate when determination of the type of epilepsy in these patients is not possible.

Lamotrigine appears to be an effective adjunctive treatment in children with the Lennox-Gastaut syndrome.[7,8]

It has also been found to be effective and well tolerated as adjunctive therapy in paediatric patients with refractory epilepsy including those with developmental impairment;[9] it was particu-

larly effective in absence and atypical seizures in this open-label study. (Evidence for the use of lamotrigine to treat absence seizures, as for the other common alternatives ethosuximide and valproate, is, however, generally poor.[10])


1. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369:** 1000–15.
2. Brodie MJ, *et al.* UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet* 1995; **345:** 476–9.
3. Ramaratnam S, *et al.* Lamotrigine add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 09/06/08).
4. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369:** 1016–26.
5. Trevathan E, *et al.* Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic-clonic seizures. Abstract: *Pediatrics* 2006; **118:** 777–8. Full version: http://www.pediatrics.org/cgi/content/full/118/2/e371 (accessed 09/06/08)
6. Biton V, *et al.* Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures. *Neurology* 2005; **65:** 1737–43.
7. Donaldson JA, *et al.* Lamotrigine adjunctive therapy in childhood epileptic encephalopathy (the Lennox Gastaut Syndrome). *Epilepsia* 1997; **38:** 68–73.
8. Motte J, *et al.* Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. *N Engl J Med* 1997; **337:** 1807–12. Correction. *ibid.* 1998; **339:** 851–2.
9. Besag FMC, *et al.* Lamotrigine for the treatment of epilepsy in childhood. *J Pediatr* 1995; **127:** 991–7.
10. Posner EB, *et al.* Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).


**Migraine.** Case reports[1] and open studies[2,3] have suggested that lamotrigine may be of benefit in the prophylaxis of migraine aura.


1. d'Onofrio F, *et al.* Basilar-type migraine responsive to lamotrigine: three case reports. *Neurol Sci* 2007; **28:** S239–S241.
2. Pascual J, *et al.* Preventing disturbing migraine aura with lamotrigine: an open study. *Headache* 2004; **44:** 1024–8.
3. Lampl C, *et al.* Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. *J Neurol Neurosurg Psychiatry* 2005; **76:** 1730–2.


**Motor neurone disease.** Lamotrigine has been tried as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p.2380) but with disappointing results.[1]


1. Ryberg H, *et al.* A double-blind randomized clinical trial in amyotrophic lateral sclerosis using lamotrigine: effects on CSF glutamate, aspartate, branched-chain amino acid levels and clinical parameters. *Acta Neurol Scand* 2003; **108:** 1–8.


**Movement disorders.** Symptomatic improvement and a trend towards decreased chorea was reported[1] with lamotrigine in a double-blind, placebo-controlled study of 64 patients with Huntington's chorea (p.953) with motor signs of less than 5 years' duration. There was, however, no clear evidence that lamotrigine retarded the progression of early Huntington disease over a period of 30 months.


1. Kremer B, *et al.* Influence of lamotrigine on progress of early Huntington disease: a randomized clinical trial. *Neurology* 1999; **53:** 1000–11.


**Neuropathic pain.** There is growing evidence that lamotrigine is of use in the management of neuropathic pain.[1] It was effective when used with carbamazepine or phenytoin in the treatment of refractory *trigeminal neuralgia*[2] (p.9), and has also shown promise in the treatment of pain associated with *HIV-related distal sensory neuropathy*[3] (p.857). Some benefit has been found[4] in the treatment of *diabetic neuropathy* (see p.6). Case reports[5] and a placebo-controlled trial[6] have also indicated that lamotrigine may be effective in *central post-stroke pain* (p.6). More recently, the use of lamotrigine in neuropathic pain has been reviewed.[7,8] Based on the same studies, one review[7] concluded that lamotrigine is an effective treatment for various types of neuropathic pain and that further studies are warranted while another[8] concluded that it is unlikely to be of benefit and that further studies are probably not justified.


1. McCleane GJ. Lamotrigine in the management of neuropathic pain: a review of the literature. *Clin J Pain* 2000; **16:** 321–6.
2. Zakrewska JM, *et al.* Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover study. *Pain* 1997; **73:** 223–30.
3. Simpson DM, *et al.* Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. *Neurology* 2003; **60:** 1508–14.
4. Eisenberg E, *et al.* Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. *Neurology* 2001; **57:** 505–9.
5. Canavero S, Bonicalzi V. Lamotrigine control of central pain. *Pain* 1996; **68:** 179–81.
6. Vestergaard K, *et al.* Lamotrigine for central post-stroke pain: a randomized controlled trial. *Neurology* 2001; **56:** 184–90.
7. Eisenberg E, *et al.* Lamotrigine for neuropathic pain. *Expert Rev Neurother* 2005; **5:** 729–35.
8. Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 09/06/08).


**Schizophrenia.** Lamotrigine has been tried as adjunctive therapy in treatment-resistant schizophrenic patients[1] and a benefit has been reported in few studies,[2-4] although patient numbers have been small. However, a systematic review[5] of the use of lamotrigine in schizophrenia concluded that the evidence for its use was poor, although it was suggestive of a positive effect on symptoms.


1. Large CH, *et al.* The potential role of lamotrigine in schizophrenia. *Psychopharmacology (Berl)* 2005; **181:** 415–36.
2. Tiihonen J, *et al.* Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. *Biol Psychiatry* 2003; **54:** 1241–8.
3. Kremer I, *et al.* Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. *Biol Psychiatry* 2004; **56:** 441–6.
4. Zoccali R, *et al.* The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. *Schizophr Res* 2007; **93:** 109–16.
5. Premkumar TS, Pick J. Lamotrigine for schizophrenia. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 09/06/08).


## Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Dafex; Epilepax; Lagotran; Lamictal; Lamirax; Lamotril; Latrigin; ***Austral.:*** Elmendos; Lamictal; Lamidus; Lamitrin; Lamogine; Seaze; ***Austria:*** Bipolam; Gerolamic; Lamictal; Lamotriglax; ***Belg.:*** Lambipol; Lamictal; ***Braz.:*** Lamictal; Lamitor; Neural; Neurium; ***Canad.:*** Lamictal; ***Chile:*** Daksol; Lafigin; Lamictal; Lomarin; Meganox; Tradox; Trizol; ***Cz.:*** Danoptin; Epimil; Epiral; Lameton; Lamictal; Lamiger; Lamogine; Lamolep; Lamotax; Lamotri; Lamotrix; Latrigil; Plexxo; Rubimar; Triginet; ***Denm.:*** Lamictal; ***Fin.:*** Lamictal; ***Fr.:*** Lamicstart; Lamictal; ***Ger.:*** Elmendos; Lamictal; Lamo; Lamotriax; Lamotrig; ***Gr.:*** Lamictal; Lamotrix; ***Hong Kong:*** Lamictal; ***Hung.:*** Epitrigine; Lamictal; Lamitrin; Lamolep; Plexxo; ***India:*** Lamepil; Lametec; ***Indon.:*** Lamictal; ***Irl.:*** Lamictal; Larig; ***Israel:*** Lamictal; Lamodex; Lamogine; ***Ital.:*** Lamictal; ***Malaysia:*** Lamictal; Lamotrix; ***Mex.:*** Lamdra; Lamictal; Limatic; Protalgine; ***Neth.:*** Lamictal; Lamitor; Lamochem†; Lamomont; Lamotifi; Plexxo†; Symla; ***Norw.:*** Lamictal; ***NZ:*** Lamictal; Mogine; ***Philipp.:*** Lamictal; ***Pol.:*** Danoptin; Epilactal; Lamia; Lamilept; Lamitrin; Lamotrihexal; Lamotrix; Plexxo; Triginet; ***Port.:*** Lamictal; ***Rus.:*** Convulsan (Конвульсан); Lamictal (Ламиктал); Lamitor (Ламитор); Lamolep (Ламолеп); ***S.Afr.:*** Epitec; Lamictin; Lamitor; ***Singapore:*** Lamictal; ***Spain:*** Crisomet; Labileno; Lamictal; ***Swed.:*** Lamictal; ***Switz.:*** Lamictal; ***Thai.:*** Lamictal; ***Turk.:*** Lamictal; ***UK:*** Lamictal; ***USA:*** Epitrogine; Lamictal; ***Venez.:*** Epifon†; Lamictal.

# Levetiracetam *(BAN, USAN, rINN)*

S-Etiracetam; Lévétiracétam; Levetiracetamum; Levetirasetam; SIB-S1; UCB-22059; UCB-L059. (S)-2-(2-Oxopyrrolidin-1-yl)butanamide.

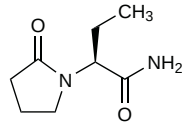
Леветирацетам

$C_8H_{14}N_2O_2$ = 170.2.

*CAS — 102767-28-2.*

*ATC — N03AX14.*

*ATC Vet — QN03AX14.*



## Adverse Effects and Precautions

The most commonly reported adverse effects associated with levetiracetam are somnolence, weakness, and dizziness. Anorexia, diarrhoea, dyspepsia, nausea, weight gain or loss, myalgia, ataxia, headache, amnesia, depression, emotional lability, insomnia, nervousness, tremor, vertigo, diplopia, and rash may occur less frequently. Other adverse effects include paraesthesia, pancreatitis, hepatic failure, and hepatitis. A raised incidence of mild infections, such as the common cold and upper respiratory-tract infections, has been reported. Alopecia may also develop; in some cases, stopping levetiracetam has resulted in regrowth of hair.

Other adverse effects reported include abnormal behaviour, aggression, anger, anxiety, confusion, hallucinations, irritability, and psychotic disorders; these adverse effects may be more common in children than in adults. Blood dyscrasias such as neutropenia, pancytopenia, and thrombocytopenia may develop.

Levetiracetam should be used with caution in patients with renal impairment, and/or severe hepatic impairment.

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

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

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

**Effects on the endocrine system.** Hyponatraemia developed[1] in a patient given levetiracetam in whom carbamazepine had previously caused the syndrome of inappropriate antidiuretic hormone secretion; symptoms resolved on stopping levetiracetam and recurred on rechallenge.


1. Nasrallah K, Silver B. Hyponatremia associated with repeated use of levetiracetam. *Epilepsia* 2005; **46:** 972–3.


**Effects on the lungs.** Diffuse interstitial lung disease developed[1] after a dose increase of levetiracetam in a 9-year-old girl who had been taking the drug for 2 years. The condition resolved when levetiracetam was stopped and treatment with corticosteroids was given.


1. Newsome SD, *et al.* Levetiracetam-induced diffuse interstitial lung disease. *J Child Neurol* 2007; **22:** 628–30.


**Effects on mental function.** For a review of the effects of antiepileptic therapy on *cognition*, and the effects of levetiracetam 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 levetiracetam than with some other antiepileptics see under Phenytoin, p.496.

**Movement disorders.** Levetiracetam has been associated with symptoms of parkinsonism including resting tremor, bradykinesia, and rigidity when used to treat Huntington's chorea in a 58-year-old man;[1] symptoms resolved within 7 days of stopping levetiracetam. The patient was also taking a number of other drugs at the time and the authors suggested that these symptoms might have been caused by a drug interaction. However, levetiracetam has been tried in the treatment of some movement disorders as discussed under Uses and Administration, below.


1. Zesiewicz TA, *et al.* Levetiracetam-induced parkinsonism in a Huntington disease patient. *Clin Neuropharmacol* 2005; **28:** 188–90.


**Overdosage.** A 38-year-old woman who ingested 30 g of levetiracetam vomited 4 hours later and presented with hypoxia, hypotension, and respiratory depression 6 hours after ingestion; peak plasma-levetiracetam concentration was 400 micrograms/mL.[1] The patient recovered without sequelae over 48 hours with symptomatic treatment.


1. Barrueto F, *et al.* A case of levetiracetam (Keppra ) poisoning with clinical and toxicokinetic data. *J Toxicol Clin Toxicol* 2002; **40:** 881–4.


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

The UK Epilepsy and Pregnancy Register[1] provided data as of July 2005 from 117 first-trimester exposures to levetiracetam with 39 to monotherapy and 78 to adjunctive therapy. In the former group, 4 infants had a low birth-weight and 4 were born at 37 weeks of gestation or less. In the latter, 10 had a low birthweight, 18 were born at 37 weeks of gestation or less, and 3 had major congenital malformations.


1. Hunt S, *et al.* Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2006; **67:** 1876–9.


## Interactions

Evidence of significant interactions between levetiracetam and other antiepileptics is mostly lacking. However, for the effects of levetiracetam on carbamazepine, see p.474.

## Pharmacokinetics

Levetiracetam is readily absorbed from the gastrointestinal tract with a bioavailability of almost 100%; peak plasma concentrations are usually achieved within 1.3 hours of oral doses and steady state achieved after 2 days. Plasma protein binding is minimal at less than 10%. Levetiracetam is not extensively metabolised; about 25% of a dose is metabolised by hydroxylation to inactive metabolites. Around 95% of a dose is excreted as unchanged drug and metabolites in the urine. The plasma elimination half-life has been reported to be about 7 hours in adults and children aged 12 years and over; the half-life may be shorter in younger children. Levetiracetam is distributed into breast milk.

◊ References.


1. Radtke RA. Pharmacokinetics of levetiracetam. *Epilepsia* 2001; **42** (suppl 4): 24–7.
2. Pellock JM, *et al.* Pharmacokinetic study of levetiracetam in children. *Epilepsia* 2001; **42:** 1574–9.
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