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.

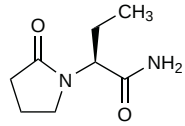
Леветирацетам

$C_8H_{14}N_2O_2$ = 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.
3. Coupez R, *et al.* Levetiracetam: relative bioavailability and bioequivalence of a 10% oral solution (750 mg) and 750-mg tablets. *J Clin Pharmacol* 2003; **43:** 1370–6.
4. Patsalos PN. Clinical pharmacokinetics of levetiracetam. *Clin Pharmacokinet* 2004; **43:** 707 24.
5. Brockmöller J, *et al.* Pharmacokinetics of levetiracetam in patients with moderate to severe liver cirrhosis (Child-Pugh classes A, B, and C): characterization by dynamic liver function tests. *Clin Pharmacol Ther* 2005; **77:** 529–41.

6. Glauser TA, *et al.* Pharmacokinetics of levetiracetam in infants and young children with epilepsy. *Epilepsia* 2007; **48:** 1117–22.
7. Tomson T, *et al.* Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007; **48:** 1111–16.
8. Hirsch LJ, *et al.* Effect of age and comedication on levetiracetam pharmacokinetics and tolerability. *Epilepsia* 2007; **48:** 1351–9.

Uses and Administration

Levetiracetam is an analogue of piracetam (p.368). It is used as an adjunct in the treatment of partial seizures with or without secondary generalisations in adults and children aged 4 years and over; in the UK, adults and adolescents aged 16 years and over may also be given levetiracetam as monotherapy for this indication. In addition, levetiracetam is licensed for adjunctive use in the treatment of myoclonic seizures in adults and children aged 12 years and over with juvenile myoclonic epilepsy. It is also licensed for use as an adjunct in the treatment of primary generalised tonic-clonic seizures in adults and children with idiopathic generalised epilepsy; for this indication, in the UK, licensed use is restricted to children aged 12 years and over, whereas in the USA, it is licensed from 6 years of age.

The daily oral dose of levetiracetam is given in two divided doses.

- The initial adult dose when used *as an adjunct* is 1 g on the first day of treatment; thereafter, the daily dose may be increased in steps of 1 g every 2 to 4 weeks until effective antiepileptic control is achieved, up to a maximum dose of 3 g daily.

  The initial dose in children weighing less than 50 kg is 20 mg/kg daily which may be increased in steps of 20 mg/kg every 2 weeks to a maximum of 60 mg/kg daily.

  Children and adolescents weighing 50 kg or more should be given the usual adult dose (see above).

  When used as *monotherapy*, the initial dose of levetiracetam is 500 mg daily, increased after 2 weeks to 1 g daily. Further increases may be made in steps of 500 mg every 2 weeks up to a maximum of 3 g daily.

When oral use is not feasible, levetiracetam may be given by intravenous infusion over 15 minutes in doses similar to those used orally; as with the oral formulation, details of licensed uses and ages may vary from country to country. UK licensed product information states that there has been no experience with the use of intravenous levetiracetam for more than 4 days.

Reduced doses are recommended in renal and severe hepatic impairment (see below).

As with other antiepileptics, withdrawal of levetiracetam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends reducing the daily dose in adults by 1 g every 2 to 4 weeks; in children, the dose reduction should not exceed 20 mg/kg every 2 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

◊ References.

1. De Smedt T, *et al.* Levetiracetam: the profile of a novel anticonvulsant drug—part I: preclinical data. *CNS Drug Rev* 2007; **13:** 43–56.
2. De Smedt T, *et al.* Levetiracetam: part II, the clinical profile of a novel anticonvulsant drug. *CNS Drug Rev* 2007; **13:** 57–78.

Administration in children. Licensed indications and doses of levetiracetam in children vary from country to country, see Uses and Administration, above. It is mainly used for partial and myoclonic seizures, and in idiopathic generalised epilepsy, often as an adjunct. A retrospective review[1] of 122 children aged from 1 month to 2 years given levetiracetam either as monotherapy (48 patients) or adjunctive therapy (74 patients) found that 70 achieved seizure remission. Of these, a longer duration of remission was seen in those receiving less than 30 mg/kg daily of levetiracetam. A case series[2] of 3 infants aged from 2 days to 3 months reported that levetiracetam 30 mg/kg daily was effective in the treatment of refractory neonatal seizures.

1. Perry MS, Benatar M. Efficacy and tolerability of levetiracetam in children younger than 4 years: a retrospective review. *Epilepsia* 2007; **48:** 1123–7.
2. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007; **22:** 95–8.

Administration in hepatic impairment. No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, creatinine clearance (CC) may underestimate concomitant renal impairment, and UK licensed product information recommends that the usual adult maintenance dose (see above) should be reduced by 50% in those with a CC of less than 70 mL/minute.

Administration in renal impairment. Reduced doses of levetiracetam are recommended for patients with renal impairment. Suitable daily doses according to UK and US licensed product information, based on creatinine clearance (CC) and given in 2 divided doses, are:

- CC 50 to 79 mL/minute: 1 to 2 g
- CC 30 to 49 mL/minute: 500 mg to 1.5 g
- CC less than 30 mL/minute: 500 mg to 1 g

Patients receiving dialysis may be given a loading dose of 750 mg when starting levetiracetam followed by doses of 500 mg to 1 g once daily; a supplemental dose of 250 to 500 mg is recommended after dialysis.

Doses may be given orally or intravenously, as necessary.

See also above for dosage recommendations in those patients with severe hepatic impairment and concomitant renal impairment.

Epilepsy. Levetiracetam is used in epilepsy (p.465) as an adjunct or monotherapy in the management of partial seizures with or without secondary generalisation.[1-6] It is also used as an adjunct in myoclonic seizures[7-9] and for generalised tonic-clonic seizures,[10] although valproate is the drug of choice in the latter where these are associated with the syndrome of primary generalised epilepsy. Levetiracetam may be considered as second-line drug for atonic or tonic seizures, and has been tried in Lennox-Gastaut syndrome and in juvenile absence epilepsy.[11] In children, levetiracetam has also been tried as adjunctive therapy for nonconvulsive status epilepticus,[12] in infantile spasms,[13] and in severe myoclonic epilepsy of infancy,[14] and as monotherapy in partial and generalised epilepsy.[15]

1. Dooley M, Plosker GL. Levetiracetam: a review of its adjunctive use in the management of partial onset seizures. *Drugs* 2000; **60:** 871–93.
2. Chaisewikul R, *et al.* Levetiracetam add-on for drug-resistant localization related (partial) epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/06/08).
3. Welty TE, *et al.* Levetiracetam: a different approach to the pharmacotherapy of epilepsy. *Ann Pharmacother* 2002; **36:** 296–304.
4. Leach JP. Levetiracetam in the management of epilepsy. *Hosp Med* 2004; **65:** 740–4.
5. Abou-Khalil B. Benefit-risk assessment of levetiracetam in the treatment of partial seizures. *Drug Safety* 2005; **28:** 871–90.
6. Steinhoff BJ, *et al.* The SKATE study: an open-label community-based study of levetiracetam as add-on therapy for adults with uncontrolled partial epilepsy. *Epilepsy Res* 2007; **76:** 6–14.
7. Crest C, *et al.* Levetiracetam in progressive myoclonic epilepsy: an exploratory study in 9 patients. *Neurology* 2004; **62:** 640–3.
8. Specchio LM, *et al.* Open label, long-term, pragmatic study on levetiracetam in the treatment of juvenile myoclonic epilepsy. *Epilepsy Res* 2006; **71:** 32–9.
9. Noachtar S, *et al.* Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. *Neurology* 2008; **70:** 607–16.
10. Berkovic SF, *et al.* Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. *Neurology* 2007; **69:** 1751–60.
11. NICE. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (issued October 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/CG020fullguideline.pdf (accessed 09/06/08)
12. Trabacca A, *et al.* Levetiracetam in nonconvulsive status epilepticus in childhood: a case report. *J Child Neurol* 2007; **22:** 639–41.
13. Mikati MA, *et al.* Response of infantile spasms to levetiracetam. *Neurology* 2008; **70:** 574–5.
14. Striano P, *et al.* An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. *Neurology* 2007; **69:** 250–4.
15. Khurana DS, *et al.* Levetiracetam monotherapy in children with epilepsy. *Pediatr Neurol* 2007; **36:** 227–30.

Movement disorders. Levetiracetam may be of benefit in some movement disorders. It has been tried in antipsychotic-induced *tardive dyskinesia*[1-3] and with equivocal benefit in levodopa-induced tardive dyskinesia[4,5] (see under Extrapyramidal Disorders on p.971). There is also limited evidence of benefit with levetiracetam for the treatment of *chorea* (p.953) in Huntington's disease[6,7] and in *paroxysmal kinesigenic choreoathetosis*.[8]

1. Konitsiotis S, *et al.* Levetiracetam in tardive dyskinesia: an open label study. *Mov Disord* 2006; **21:** 1219–21.
2. Meco G, *et al.* Levetiracetam in tardive dyskinesia. *Clin Neuropharmacol* 2006; **29:** 265–8.
3. Woods SW, *et al.* Effects of levetiracetam on tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2008; **69:** 546–54.
4. Zesiewicz TA, *et al.* Open-label pilot study of levetiracetam (Keppra) for the treatment of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 2005; **20:** 1205–9.
5. Lyons KE, Pahwa R. Efficacy and tolerability of levetiracetam in Parkinson disease patients with levodopa-induced dyskinesia. *Clin Neuropharmacol* 2006; **29:** 148–53.
6. Zesiewicz TA, *et al.* Open-label pilot study of levetiracetam (Keppra) for the treatment of chorea in Huntington's disease. *Mov Disord* 2006; **21:** 1998–2001.
7. de Tommaso M, *et al.* Efficacy of levetiracetam in Huntington disease. *Clin Neuropharmacol* 2005; **28:** 280–4.
8. Chatterjee A, *et al.* Levetiracetam in the treatment of paroxysmal kinesiogenic choreoathetosis. *Mov Disord* 2002; **17:** 614–15.

Muscle spasm. Levetiracetam has been tried with some success in *Meige's syndrome*,[1] and *hemifacial spasm*.[2] For use in *stiff-man syndrome* see below.

1. Yardimci N, *et al.* Levetiracetam in Meige's syndrome. *Acta Neurol Scand* 2006; **114:** 63–6.
2. Deleu D. Levetiracetam in the treatment of idiopathic hemifacial spasm. *Neurology* 2004; **62:** 2134–5.

Psychiatric disorders. Levetiracetam has psychotropic properties and has been tried in the management of *anxiety disorders*[1] (p.952) including *social anxiety disorder*[2] (see Phobic Disorders, p.953), *post-traumatic stress disorder*[3] (p.953), and *panic disorder*[4] (p.952). There is also limited evidence[5] from case reports and small open-label studies that levetiracetam may be of benefit in the treatment of *bipolar disorder* (p.372).

1. Kinrys G, *et al.* Levetiracetam as adjunctive therapy for refractory anxiety disorders. *J Clin Psychiatry* 2007; **68:** 1010–13.
2. Simon NM, *et al.* An open-label study of levetiracetam for the treatment of social anxiety disorder. *J Clin Psychiatry* 2004; **65:** 1219–22.
3. Kinrys G, *et al.* Levetiracetam for treatment-refractory posttraumatic stress disorder. *J Clin Psychiatry* 2006; **67:** 211–14.
4. Papp LA. Safety and efficacy of levetiracetam for patients with panic disorder: results of an open-label, fixed-flexible dose study. *J Clin Psychiatry* 2006; **67:** 1573–6.
5. Muralidharan A, Bhagwagar Z. Potential of levetiracetam in mood disorders: a preliminary review. *CNS Drugs* 2006; **20:** 969–79.

Restless legs syndrome. Levetiracetam has been reported to be of benefit in the treatment of refractory restless legs syndrome (see Sleep-associated Movement Disorders, p.958).[1]

1. Della Marca G, *et al.* Levetiracetam can be effective in the treatment of restless legs syndrome with periodic limb movements in sleep: report of two cases. *J Neurol Neurosurg Psychiatry* 2006; **77:** 566–7.

Status epilepticus. Levetiracetam has been tried, with some success, in the management of nonconvulsive status epilepticus[1] and refractory status epilepticus.[2] For the conventional management of status epilepticus see p.469.

1. Rupprecht S, *et al.* Levetiracetam as a treatment option in nonconvulsive status epilepticus. *Epilepsy Res* 2007; **73:** 238–44.
2. Patel NC, *et al.* The use of levetiracetam in refractory status epilepticus. *Seizure* 2006; **15:** 137–41.

Stiff-man syndrome. In a report[1] of a patient with stiff-man syndrome, substitution of levetiracetam for previous valproate therapy (because of suspected valproate-induced parkinsonism) resulted in complete suppression of paroxysmal spasms; benefit was sustained with continued therapy over 2 years of follow-up.

1. Rüegg SJ, *et al.* Levetiracetam improves paroxysmal symptoms in a patient with stiff-person syndrome. *Neurology* 2004; **62:** 338.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p.1231); however, levetiracetam has also been tried with some success.[1] Benefit was also reported[2] with levetiracetam in the treatment of tremor secondary to multiple sclerosis.

1. Bushara KO, *et al.* The effect of levetiracetam on essential tremor. *Neurology* 2005; **64:** 1078–80.
2. Striano P, *et al.* Levetiracetam for cerebellar tremor in multiple sclerosis: an open-label pilot tolerability and efficacy study. *J Neurol* 2006; **253:** 762–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Keppra; Levron; ***Austral.:*** Keppra; ***Belg.:*** Keppra; ***Canad.:*** Keppra; ***Chile:*** Kopodex; ***Cz.:*** Keppra; ***Denm.:*** Keppra; ***Fin.:*** Keppra; ***Fr.:*** Keppra; ***Ger.:*** Keppra; ***Gr.:*** Keppra; ***Hong Kong:*** Keppra; ***Hung.:*** Keppra; ***India:*** Levroxa; ***Indon.:*** Keppra; ***Irl.:*** Keppra; ***Israel:*** Keppra; ***Ital.:*** Keppra; ***Malaysia:*** Keppra; ***Mex.:*** Keppra; ***Neth.:*** Keppra; ***Norw.:*** Keppra; ***NZ:*** Keppra; ***Philipp.:*** Keppra; ***Pol.:*** Keppra; ***Port.:*** Keppra; ***Rus.:*** Keppra (Кеппра); ***S.Afr.:*** Keppra; ***Singapore:*** Keppra; ***Spain:*** Keppra; ***Swed.:*** Keppra; ***Switz.:*** Keppra; ***Thai.:*** Keppra; ***Turk.:*** Keppra; ***UK:*** Keppra; ***USA:*** Keppra.

Losigamone *(rINN)*

AO-33; Losigamona; Losigamonum. (5*R**)-5-[(α*S**)-o-Chloro-α-hydroxybenzyl]-4-methoxy-2(5*H*)-furanone.

Лозигамон

$C_{12}H_{11}ClO_4$ = 254.7.
CAS — 112856-44-7.