Profile
Losigamone is an antiepileptic that has been investigated as adjunctive therapy in the treatment of partial seizures.

◊ References

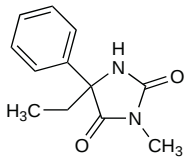
1. Bauer J, *et al*. Losigamone add-on therapy in partial epilepsy: a placebo-controlled study. *Acta Neurol Scand* 2001; **103:** 226–30.
2. Baulac M, Klement S. Losigamone Study Group. Efficacy and safety of losigamone in partial seizures: a randomized double-blind study. *Epilepsy Res* 2003; **55:** 177–89.

Mephenytoin *(BAN, USAN, rINN)*

Mefenitoína; Mefenytoiini; Mefenytoin; Mephenetoin; Méphénytoïne; Mephenytoinum; Methantoin; Methoin; NSC-34652; Phenantoin. 5-Ethyl-3-methyl-5-phenylhydantoin.

Мефенитоин

$C_{12}H_{14}N_2O_2$ = 218.3.
CAS — 50-12-4.
ATC — N03AB04.
ATC Vet — QN03AB04.



Pharmacopoeias. In *US*.
USP 31 (Mephenytoin). Store in airtight containers.

Profile
Mephenytoin is a hydantoin antiepileptic with actions similar to those of phenytoin (p.495), but it is more toxic. Because of its potential toxicity it is not one of the main drugs used in the treatment of epilepsy (p.465) and is given only to patients unresponsive to other treatment. Some of the adverse effects of mephenytoin may be due to the metabolite, 5-ethyl-5-phenylhydantoin (also termed nirvanol). Like phenytoin the rate of metabolism of mephenytoin is subject to genetic polymorphism.

Mephenytoin is given in an initial oral daily dose of 50 to 100 mg for 1 week; thereafter the daily dose is increased by 50 to 100 mg at weekly intervals until the optimum dose is reached, which is usually between 200 and 600 mg daily for an adult and 100 and 400 mg daily for a child; daily maintenance doses are usually taken in 3 divided doses.

Porphyria. Mephenytoin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations
USP 31: Mephenytoin Tablets.

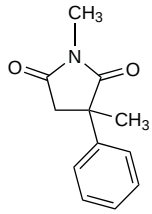
Proprietary Preparations (details are given in Part 3)
Austria: Epilan; ***Cz.:*** Epilan†.

Mesuximide *(BAN, rINN)*

Mesuksimidi; Mesuximid; Mesuximida; Mésuximide; Mesuximidum; Methsuximide; PM-396. *N*,2-Dimethyl-2-phenylsuccinimide.

Мезуксимид

$C_{12}H_{13}NO_2$ = 203.2.
CAS — 77-41-8.
ATC — N03AD03.
ATC Vet — QN03AD03.



Pharmacopoeias. In *US*.
USP 31 (Methsuximide). A white to greyish-white crystalline powder. Is odourless or has a slight odour. Soluble 1 in 350 of water, 1 in 3 of alcohol, 1 in less than 1 of chloroform, and 1 in 2 of ether. Store in airtight containers.

Profile
Mesuximide is a succinimide antiepileptic with actions similar to those of ethosuximide (p.479) that is used in the treatment of absence seizures; although it also has some activity in complex partial seizures it is reported to be less well tolerated than ethosuximide, and is usually only given to patients unresponsive to other antiepileptic treatment. It is thought to owe its activity to its major metabolite *N*-desmethylmesuximide.

The usual initial oral dosage is a single dose of 300 mg daily for the first week, and this is increased by 300 mg at weekly intervals to an optimum dosage, according to response. The suggested maximum daily dose is 1.2 g in divided doses.

Epilepsy. Mesuximide is used for absence seizures that are refractory to less toxic antiepileptics such as ethosuximide or valproate, which are the usual first-line drugs (see p.465). Mesuximide has also been tried in complex partial seizures and myoclonic seizures.

References.

1. Tennison MB, *et al*. Methsuximide for intractable childhood seizures. *Pediatrics* 1991; **87:** 186–9.
2. Sigler M, *et al*. Effective and safe but forgotten: methsuximide in intractable epilepsies in childhood. *Seizure* 2001; **10:** 120–4.

Interactions. For the effect of mesuximide on lamotrigine and valproate, see p.486 and p.511 respectively.

Porphyria. Mesuximide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations
USP 31: Methsuximide Capsules.

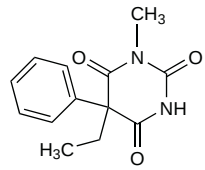
Proprietary Preparations (details are given in Part 3)
Austria: Petinutin; ***Canad.:*** Celontin; ***Ger.:*** Petinutin; ***Israel:*** Celontin†; ***Neth.:*** Celontin; ***Switz.:*** Petinutin; ***USA:*** Celontin.

Methylphenobarbital *(BAN, rINN)*

Enphenemalum; Mephobarbital; Methylfenobarbital; Méthylphénobarbital; Methylphenobarbitalum; Methylphenobarbitone; Metilfenobarbitál; Metilfenobarbital; Metilfenobarbitalis; Metylfenobarbital; Metyylifenobarbitaali; Phemitone. 5-Ethyl-1-methyl-5-phenylbarbituric acid.

Метилфенобарбитал

$C_{13}H_{14}N_2O_3$ = 246.3.
CAS — 115-38-8.
ATC — N03AA01.
ATC Vet — QN03AA01.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Methylphenobarbital). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; very slightly soluble in dehydrated alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.
USP 31 (Mephobarbital). A white, odourless, crystalline powder. Slightly soluble in water, in alcohol, and in ether; soluble in chloroform and in solutions of fixed alkali hydroxides and carbonates. Its saturated solution in water is acid to litmus.

Dependence and Withdrawal, Adverse Effects, Treatment, and Precautions
As for Phenobarbital, p.492.

Interactions
As for Phenobarbital, p.493.

Pharmacokinetics
Methylphenobarbital is incompletely absorbed from the gastrointestinal tract. It is demethylated to phenobarbital (p.494) in the liver.

Uses and Administration
Methylphenobarbital is used similarly to phenobarbital (p.494) in the treatment of epilepsy (p.465). It is given in oral doses of up to 600 mg daily. It has also been used as a sedative in a usual dose of 50 mg 3 or 4 times daily.

Preparations
BP 2008: Methylphenobarbital Tablets;
USP 31: Mephobarbital Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Prominal†; ***USA:*** Mebaral.

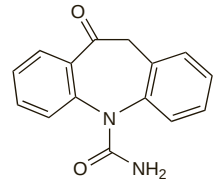
Multi-ingredient: ***Arg.:*** Cumatil L; ***Ital.:*** Dintoinale; Metinal-Idantoina; Metinal-Idantoina L.

Oxcarbazepine *(BAN, USAN, rINN)*

GP-47680; KIN-493; Okskarbatsepiini; Okskarbazepin; Oxcarbazepin; Oxcarbazepina; Oxcarbazépine; Oxcarbazepinum. 10,11-Dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide.

Окскарбазепин

$C_{15}H_{12}N_2O_2$ = 252.3.
CAS — 28721-07-5.
ATC — N03AF02.
ATC Vet — QN03AF02.



Adverse Effects, Treatment, and Precautions
As for Carbamazepine, p.472.

Hypersensitivity reactions such as skin rashes (see also under Carbamazepine, p.473) occur less frequently with oxcarbazepine than with carbamazepine. However, cross-sensitivity does occur and about 25 to 30% of patients hypersensitive to carbamazepine may experience such reactions with oxcarbazepine. Reductions in plasma-sodium levels have also been observed with oxcarbazepine (see Hyponatraemia, below). Patients with cardiac insufficiency and secondary heart failure should be weighed regularly to detect fluid retention. Oxcarbazepine may, very rarely, impair cardiac conduction and patients with pre-existing conduction disorders should be carefully monitored. Very rarely, oxcarbazepine treatment has been associated with pancreatitis.

Dosage reductions are recommended in renal impairment.

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 blood. Although it would appear that oxcarbazepine is less likely than carbamazepine to cause blood dyscrasias such as leucopenia, individual cases have been reported. In one such case leucopenia and hyponatraemia developed in a 57-year-old woman while taking oxcarbazepine;[1] she recovered after treatment with filgrastim. It was noted that the patient had experienced a similar reaction when taking carbamazepine. Oxcarbazepine has also been associated with reversible pancytopenia[2] in a 40-year-old woman, and reversible thrombocytopenia[3] in a 63-year-old woman.

1. Ryan M, *et al*. Hyponatremia and leukopenia associated with oxcarbazepine following carbamazepine therapy. *Am J Health-Syst Pharm* 2001; **58:** 1637–9.
2. Calamaras MR, *et al*. Pancytopenia associated with the introduction of oxcarbazepine. *J Clin Psychopharmacol* 2007; **27:** 217–18.
3. Mahmud J, *et al*. Oxcarbazepine-induced thrombocytopenia. *Psychosomatics* 2006; **47:** 73–4.

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

Effects on sexual function. For mention of the effects of antiepileptics including oxcarbazepine on sexual function in male epileptic patients, see Effects on the Endocrine System, under Phenytoin, p.496.

Hyponatraemia. Hyponatraemia appears to be more pronounced at clinical doses of oxcarbazepine than with carbamazepine. Hyponatraemia was reported[1] in 12 of 15 patients in whom oxcarbazepine was substituted for carbamazepine therapy. The fall in plasma-sodium concentrations appeared to be related to the dose of oxcarbazepine. In another report[2] hyponatraemia occurred in 23% of 350 patients whose serum-sodium concentrations were monitored. The manufacturers state that in 14 controlled studies sodium levels of less than 125 mmol/litre occurred in 2.5% of 1524 patients treated with oxcarbazepine compared to no such patients in the control groups. Most patients remain asymptomatic but some may experience drowsiness, increase in seizure frequency, and impaired consciousness.[3] In a later study[4] in 97 patients taking oxcarbazepine and 451 taking carbamazepine, hyponatraemia occurred in 29 (12 severe) of the former and in 61 (13 severe) of the latter. The authors failed to

find a correlation between high doses of oxcarbazepine and the occurrence of hyponatraemia.

It has been suggested that serum-sodium concentrations should be measured before the start of therapy but routine monitoring, may be indicated only in elderly patients or if a high dosage is used.[5] Licensed product information recommends that monitoring be considered in those with pre-existing conditions associated with low sodium levels and in those taking other medications known to interfere with sodium levels, for example NSAIDs and diuretics.

Severe hyponatraemia has been reported[6] in a 12-year-old child during treatment with oxcarbazepine. A review of 48 other children who had received oxcarbazepine in the same centre, found that 9 had hyponatraemia, and the authors suggested that sodium levels should be monitored in paediatric patients. In another case,[7] a 7-year old boy developed a reversible coma caused by oxcarbazepine-induced hyponatraemia.

1. Pendlebury SC, *et al.* Hyponatraemia during oxcarbazepine therapy. *Hum Toxicol* 1989; **8:** 337–44.
2. Friis ML, *et al.* Therapeutic experiences with 947 epileptic outpatients in oxcarbazepine treatment. *Acta Neurol Scand* 1993; **87:** 224–7.
3. Steinhoff BJ, *et al.* Hyponatraemic coma under oxcarbazepine therapy. *Epilepsy Res* 1992; **11;** 67–70.
4. Dong X, *et al.* Hyponatremia from oxcarbazepine and carbamazepine. *Neurology* 2005; **65:** 1976–8.
5. Kälviäinen R, *et al.* Place of newer antiepileptic drugs in the treatment of epilepsy. *Drugs* 1993; **46:** 1009–24.
6. Borusiak P, *et al.* Hyponatremia induced by oxcarbazepine in children. *Epilepsy Res* 1998; **30:** 241–6.
7. Paliwal V, *et al.* Oxcarbazepine induced hyponatremic coma. *Neurol India* 2006; **54:** 214–15.

Overdosage. A 36-year-old man[1] who ingested 30.6 g of oxcarbazepine showed no serious signs of toxicity. Serum concentrations of oxcarbazepine were 31.6 mg/litre 2 hours after ingestion; corresponding serum concentrations of the active monohydroxy metabolite were 37.2 mg/litre, which later peaked at 59.0 mg/litre 7 hours after ingestion. The patient remained conscious, though somnolent, and had fully recovered within 2 days.

1. van Opstal JM, *et al.* Severe overdosage with the antiepileptic drug oxcarbazepine. *Br J Clin Pharmacol* 2004; **58:** 329–31.

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

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. Plasma concentrations of the active monohydroxy metabolite of oxcarbazepine may be reduced by strong inducers of cytochrome P450 isoenzymes, such as carbamazepine, phenytoin, or phenobarbital. Oxcarbazepine appears to induce hepatic enzymes to a lesser extent than carbamazepine. However, oxcarbazepine and its active metabolite do inhibit the cytochrome P450 isoenzyme CYP2C19, and in high doses may raise plasma concentrations of phenobarbital or phenytoin. Oxcarbazepine and its metabolite also have the capacity to induce CYP3A4 and CYP3A5 with the possibility of reducing plasma concentrations of drugs such as carbamazepine (but see below), dihydropyridine calcium-channel blockers, and oral contraceptives.

◊ References.

1. Sallas WM, *et al.* Pharmacokinetic drug interactions in children taking oxcarbazepine. *Clin Pharmacol Ther* 2003; **74:** 138–49.

Antiepileptics. In a study[1] of epileptic patients the area under the concentration-time curve (AUC) seen with monotherapy of *carbamazepine*, *phenytoin*, or *valproate* was unchanged when oxcarbazepine was added to treatment; only carbamazepine affected the pharmacokinetics of oxcarbazepine, producing a reduction in the AUC for the active metabolite hydroxycarbazepine. It was considered that there was unlikely to be any clinically relevant pharmacokinetic interaction if oxcarbazepine was used with any of these antiepileptics, including carbamazepine. However, increases in plasma-phenytoin concentration have been reported after use with oxcarbazepine (see p.498).

There is a case-report of severe toxicity occurring with concomitant use of oxcarbazepine and *lamotrigine*.[2] For the effect of oxcarbazepine on lamotrigine concentrations, see p.486.

1. McKee PJW, *et al.* A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. *Br J Clin Pharmacol* 1994; **37:** 27–32.
2. Alving J. Case of severe acute intoxication with oxcarbazepine combined with lamotrigine. *Epilepsia* 1994; **35** (suppl 7): 72.

Pharmacokinetics

Oxcarbazepine is completely absorbed from the gastrointestinal tract. It is rapidly and extensively metabolised in the liver to the principal metabolite 10,11-dihydro-10-hydroxy-carbamazepine, often referred to as MHD, which also possesses antiepileptic activity. The monohydroxy metabolite is widely distributed in the body and is about 40% bound to plasma proteins, mainly albumin. The plasma half-life has been reported to be about 2 hours for oxcarbazepine, and about 9 hours for the monohydroxy metabolite; consequently the latter provides most of the antiepileptic activity. Clearance of the monohydroxy metabolite is reported to be about 40% higher in children aged 4 to 12 years, and about 80% higher in those aged 2 to 4 years, than in adults. Oxcarbazepine is excreted in the urine mainly as metabolites; less than 1% is excreted as unchanged drug.

Oxcarbazepine and its monohydroxy metabolite cross the placental barrier and are distributed into breast milk.

The pharmacokinetics of oxcarbazepine and its monohydroxy metabolite are affected by use with other antiepileptics (see Interactions, above).

◊ References.

1. Dickinson RG, *et al.* First dose and steady-state pharmacokinetics of oxcarbazepine and its 10-hydroxy metabolite. *Eur J Clin Pharmacol* 1989; **37:** 69–74.
2. Patsalos PN, *et al.* Protein binding of oxcarbazepine and its primary active metabolite, 10-hydroxycarbazepine, in patients with trigeminal neuralgia. *Eur J Clin Pharmacol* 1990; **39:** 413–15.
3. Kumps A, Wurth C. Oxcarbazepine disposition: preliminary observations in patients. *Biopharm Drug Dispos* 1990; **11:** 365–70.
4. van Heiningen PNM, *et al.* The influence of age on the pharmacokinetics of the antiepileptic agent oxcarbazepine. *Clin Pharmacol Ther* 1991; **50:** 410–19.
5. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
6. May TW, *et al.* Clinical pharmacokinetics of oxcarbazepine. *Clin Pharmacokinet* 2003; **42:** 1023–42.
7. Rey E, *et al.* Oxcarbazepine pharmacokinetics and tolerability in children with inadequately controlled epilepsy. *J Clin Pharmacol* 2004; **44:** 1290–1300.
8. Flesch G. Overview of the clinical pharmacokinetics of oxcarbazepine. *Clin Drug Investig* 2004; **24:** 185–203.

Pregnancy. Clearance of the active monohydroxy metabolite of oxcarbazepine was reported to increase[1,2] during pregnancy and to decrease[2] after delivery; one study[1] reported a reduction in plasma concentrations of about 36% during the third trimester. However, sample sizes in both studies were small.

1. Christensen J, *et al.* Oxcarbazepine concentrations during pregnancy: a retrospective study in patients with epilepsy. *Neurology* 2006; **67:** 1497–9.
2. Mazzucchelli I, *et al.* Changes in the disposition of oxcarbazepine and its metabolites during pregnancy and the puerperium. *Epilepsia* 2006; **47:** 504–9.

Uses and Administration

Oxcarbazepine is a derivative of carbamazepine (p.476) with similar actions. It is used as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. The initial oral dose for monotherapy and adjunctive therapy is 600 mg daily, given in 2 divided doses. The daily dose may be increased thereafter, if necessary, in maximum increments of 600 mg at approximately weekly intervals until the desired clinical response has been achieved. Maintenance doses are usually in the range of 600 mg to 1.2 g daily or up to 2.4 g daily if given as adjunctive therapy or in refractory patients switched from other antiepileptics.

For doses in children, see below.

Reduced initial doses are recommended in patients with renal impairment (see below).

As with other antiepileptics, withdrawal of oxcarbazepine 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.

Administration in children. Oxcarbazepine is used in children as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. In the UK, the recommended initial oral dose for monotherapy and adjunctive therapy in those aged 6 years and over is 8 to 10 mg/kg daily, given in 2 divided doses. The daily dose may be increased thereafter, if necessary, in maximum increments of 10 mg/kg at approximately weekly intervals to a maximum dose of 46 mg/kg daily; usual maintenance doses in adjunctive therapy are around 30 mg/kg daily. In the USA, similar doses are recommended for adjunctive therapy in children aged 2 years and over (the initial dose may be doubled in those weighing under 20 kg), and for monotherapy in those aged 4 years and over; a maximum daily dose of 60 mg/kg is permitted for adjunctive therapy.

Administration in renal impairment. Initial doses of oxcarbazepine for adult patients with a creatinine clearance of less than 30 mL/minute should be 300 mg daily (half the usual starting dose, above), increased at weekly intervals or longer.

Bipolar disorder. Like the related drug carbamazepine (p.476), oxcarbazepine has antimanic properties and has been tried in the management of patients with bipolar disorder (p.372). Reviews[1,2] have suggested that it may be useful in treating acute mania and in patients with refractory disease; however, the evidence base is weak[3] and further studies are needed.

1. Pratoomsri W, *et al.* Oxcarbazepine in the treatment of bipolar disorder: a review. *Can J Psychiatry* 2006; **51:** 540–5.
2. Popova E, *et al.* Oxcarbazepine in the treatment of bipolar and schizoaffective disorders. *Expert Rev Neurother* 2007; **7:** 617–26.
3. Vasudev A, *et al.* Oxcarbazepine in the maintenance treatment of bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/06/08).

Epilepsy. Oxcarbazepine is used in the treatment of epilepsy (p.465) and may be a useful alternative in patients unable to tolerate carbamazepine.

In a double-blind study[1] involving newly diagnosed adult patients, oxcarbazepine was of similar efficacy and tolerability to valproate for partial or generalised tonic-clonic seizures. Oxcarbazepine was of similar efficacy to phenytoin, but was better tolerated in adults and children with newly diagnosed partial or generalised tonic-clonic seizures.[2,3] Further randomised controlled studies and 2 small systematic reviews[4,5] have also confirmed the efficacy and tolerability of oxcarbazepine as adjunctive therapy[4,6] or monotherapy[5,7-9] in refractory partial seizures in children and adults.

1. Christe W, *et al.* A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. *Epilepsy Res* 1997; **26:** 451–60.
2. Bill PA, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. *Epilepsy Res* 1997; **27:** 195–204.
3. Guerreiro MM, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. *Epilepsy Res* 1997; **27:** 205–13.
4. Castillo S, *et al.* Oxcarbazepine add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 09/06/08).
5. Muller M, *et al.* Oxcarbazepine versus phenytoin monotherapy for epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 09/06/08).
6. Glauser TA, *et al.* Adjunctive therapy with oxcarbazepine in children with partial seizures. *Neurology* 2000; **54:** 2237–44.
7. Beydoun A, *et al.* Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. *Neurology* 2000; **54:** 2245–51.
8. Sachdeo R, *et al.* Oxcarbazepine (Trileptal) as monotherapy in patients with partial seizures. *Neurology* 2001; **57:** 864–71.
9. Herranz Fernández JL, *et al.* Oxcarbacepina en monoterapia en 324 pacientes con crisis parciales (estudio TRINOVA). *Rev Neurol* 2004; **39:** 601–6.

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). Carbamazepine appears to be the antiepileptic most frequently used, but oxcarbazepine has also been tried in various neuropathic pain syndromes[1] including painful diabetic neuropathy[2-4] (see p.6), postherpetic neuralgia[5,6] (p.9), complex regional pain syndrome[7] (p.6), glossopharyngeal neuralgia,[8] oxaliplatin-induced neuropathy[9] (see p.758), and trigeminal neuralgia (p.9).

1. Magenta P, *et al.* Oxcarbazepine is effective and safe in the treatment of neuropathic pain: pooled analysis of seven clinical studies. *Neurol Sci* 2005; **26:** 218–26.
2. Dogra S, *et al.* Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. *Eur J Pain* 2005; **9:** 543–54.
3. Grosskopf J, *et al.* A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy. *Acta Neurol Scand* 2006; **114:** 177–80.
4. Beydoun S, *et al.* Long-term safety and tolerability of oxcarbazepine in painful diabetic neuropathy. *Acta Neurol Scand* 2007; **115:** 284–8.
5. Criscuolo S, *et al.* Oxcarbazepine (Trileptal) monotherapy dramatically improves quality of life in two patients with postherpetic neuralgia refractory to carbamazepine and gabapentin. *J Pain Symptom Manage* 2004; **28:** 535–6.
6. Criscuolo S, *et al.* Oxcarbazepine monotherapy in postherpetic neuralgia unresponsive to carbamazepine and gabapentin. *Acta Neurol Scand* 2005; **111:** 229–32.
7. Lalwani K, *et al.* Use of oxcarbazepine to treat a pediatric patient with resistant complex regional pain syndrome. *J Pain* 2005; **6:** 704–6.
8. Luef G, Poewe W. Oxcarbazepine in glossopharyngeal neuralgia: clinical response and effect on serum lipids. *Neurology* 2004; **63:** 2447–8.
9. Argyriou AA, *et al.* Efficacy of oxcarbazepine for prophylaxis against cumulative oxaliplatin-induced neuropathy. *Neurology* 2006; **67:** 2253–5.

Psychiatric disorders. Case reports[1,2] in children and adolescents and a randomised, placebo-controlled study[3] in adults have indicated some benefit from oxcarbazepine in the treatment of *aggression* and *disturbed behaviour*(p.954). A retrospective review[4] of 14 children and adolescents with various psychiatric and behavioural disorders found moderate symptomatic improvement in 50% after the addition of oxcarbazepine. Oxcarbazepine has also been tried in the treatment of *schizophrenia*[5] (p.955) and *post-traumatic stress disorder*[6] (p.953). For use in *bipolar disorder* see above.

1. Kapetanovic S. Oxcarbazepine in youths with autistic disorder and significant disruptive behaviors. *Am J Psychiatry* 2007; **164:** 832–3.
2. Gaudino MP, *et al.* Use of oxcarbazepine for treatment-resistant aggression. *Psychiatr Serv* 2003; **54:** 1166–7.
3. Mattes JA. Oxcarbazepine in patients with impulsive aggression: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2005; **25:** 575–9.
4. Staller JA, *et al.* Oxcarbazepine in the treatment of child psychiatric disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol* 2005; **15:** 964–9.
5. Leweke FM, *et al.* Oxcarbazepine as an adjunct for schizophrenia. *Am J Psychiatry* 2004; **161:** 1130–1.
6. Malek-Ahmadi P, Hanretta AT. Possible reduction in posttraumatic stress disorder symptoms with oxcarbazepine in a patient with bipolar disorder. *Ann Pharmacother* 2004; **38:** 1852–4.

Withdrawal syndromes and abstinence. Oxcarbazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Although it was not found[1] to be superior to placebo in the treatment of symptoms of the *alcohol withdrawal syndrome* (p.1626), oxcarbazepine has been reported[2-4] to be of benefit in relapse prevention; further studies are considered warranted. It has also been tried[5] during *benzodiazepine withdrawal* but such adjunct therapy is not usually indicated (see p.987).

1. Koethe D, *et al.* Oxcarbazepine—efficacy and tolerability during treatment of alcohol withdrawal: a double-blind, randomized, placebo-controlled multicenter pilot study. *Alcohol Clin Exp Res* 2007; **31:** 1188–94.
2. Croissant B, *et al.* Oxcarbazepine in alcohol relapse prevention: a case series. *Pharmacopsychiatry* 2004; **37:** 306–7.
3. Croissant B, *et al.* A pilot study of oxcarbazepine versus acamprosate in alcohol-dependent patients. *Alcohol Clin Exp Res* 2006; **30:** 630–5.
4. Martinotti G, *et al.* High and low dosage oxcarbazepine versus naltrexone for the prevention of relapse in alcohol-dependent patients. *Hum Psychopharmacol* 2007; **22:** 149–56.
5. Croissant B, *et al.* Scheme-based benzodiazepine detoxification with oxcarbazepine: a case report. *Pharmacopsychiatry* 2005; **38:** 222–3.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Atoxecar†; Aurene; Oxca; Oxcazen†; Rupox; Trileptal; ***Austral.:*** Trileptal; ***Austria:*** Trileptal; ***Belg.:*** Trileptal; ***Braz.:*** Auram; Oleptal; Oxcarb; Trileptal; ***Canad.:*** Trileptal; ***Chile:*** Alox†; Oxicodal; Trileptal; ***Cz.:*** Trileptal; ***Denm.:*** Apydan; Trileptal; ***Fin.:*** Apydan; Trileptal; ***Fr.:*** Trileptal; ***Ger.:*** Timox; Trileptal; ***Gr.:*** Trileptal; ***Hong Kong:*** Trileptal; ***Hung.:*** Apydan; Trileptal; ***India:*** Oxcarb; Oxrate; ***Indon.:*** Barzepin; Prolepsi; Trileptal; ***Irl.:*** Trileptal; ***Israel:*** Trileptin; ***Ital.:*** Tolep; ***Malaysia:*** Trileptal; ***Mex.:*** Actinium; Deprectal; Oxetol; Trileptal; ***Neth.:*** Trileptal; ***Norw.:*** Trileptal; ***NZ:*** Trileptal; ***Philipp.:*** Trileptal; ***Pol.:*** Apydan; Trileptal; ***Port.:*** Epilfarmo; Proaxen; Zigabal; ***Rus.:*** Trileptal (Трилептал); ***S.Afr.:*** Trileptal; ***Spain:*** Trileptal; ***Swed.:*** Trileptal; ***Switz.:*** Trileptal; ***Thai.:*** Trileptal; ***Turk.:*** Trileptal; ***UK:*** Trileptal; ***USA:*** Trileptal; ***Venez.:*** Trileptal.

Pheneturide *(BAN, rINN)*

Ethylphenacemide; Feneturida; Phénéturide; Pheneturidum; S-46. (2-Phenylbutyryl)urea.

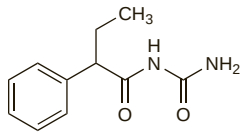
Фенетурид

$C_{11}H_{14}N_2O_2$ = 206.2.

CAS — 90-49-3.

ATC — N03AX13.

ATC Vet — QN03AX13.



Profile

Pheneturide is an acetylurea antiepileptic used in the treatment of complex partial seizures with or without secondary generalisation (p.465). It is given in usual oral daily doses of 300 to 600 mg in 2 or 3 divided doses, up to a maximum of 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Laburide.

Phenobarbital *(BAN, rINN)*

Ácido feniletilbarbitúrico; Fenobarbitaali; Fenobarbitál; Fenobarbital; Fenobarbitalis; Fenobarbitona; Phenemalum; Phénobarbital; Phenobarbitalum; Phenobarbitone; Phenylethylbarbituric Acid; Phenylethylmalonylurea. 5-Ethyl-5-phenylbarbituric acid.

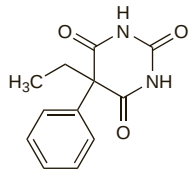
Фенобарбитал

$C_{12}H_{12}N_2O_3$ = 232.2.

CAS — 50-06-6.

ATC — N03AA02.

ATC Vet — QN03AA02.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of phenobarbital: Feenies; Phennies; Phenos.

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

Ph. Eur. 6.2 (Phenobarbital). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; freely soluble in alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 31 (Phenobarbital). White, odourless, glistening, small crystals or a white crystalline powder. It may exhibit polymorphism. Soluble 1 in 1000 of water and 1 in 10 of alcohol; sparingly soluble in chloroform; soluble in ether and in solutions of fixed alkali hydroxides and carbonates. A saturated solution in water has a pH of about 5.

Phenobarbital Sodium *(BANM, rINN)*

Fenobarbitaalinatrium; Fenobarbital sódico; Fenobarbital sodná sůl; Fenobarbital sodowy; Fenobarbitalio natrio druska; Fenobarbitalnatrium; Fenobarbitál-nátrium; Natrii Phenobarbitalum; Phenemalnatrium; Phénobarbital sodique; Phenobarbitalum natricum; Phenobarbitone Sodium; Sodium Phenylethylbarbiturate; Soluble Phenobarbitone. Sodium 5-ethyl-5-phenylbarbiturate.

Натрий Фенобарбитал

$C_{12}H_{11}N_2NaO_3$ = 254.2.

CAS — 57-30-7.

ATC — N03AA02.

ATC Vet — QN03AA02.

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

Ph. Eur. 6.2 (Phenobarbital Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in carbon dioxide-free water (a small amount may be insoluble); soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH not greater than 10.2. Store in airtight containers.

USP 31 (Phenobarbital Sodium). Flaky crystals, or white crystalline granules, or a white powder. It is odourless and hygroscopic. Very soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 10% solution in water is between 9.2 and 10.2. Solutions decompose on standing. Store in airtight containers.

Incompatibility. Phenobarbital sodium is incompatible with many other drugs and phenobarbital may be precipitated from mixtures containing phenobarbital sodium. This precipitation is dependent upon the concentration and the pH, and also on the presence of other solvents.

Stability. Extemporaneous oral preparations of phenobarbital 10 mg/mL in a 1:1 mixture of *Ora-Plus* and either *Ora-Sweet* or *Ora-Sweet SF* (*Paddock, USA*) were found[1] to be stable for at least 115 days in amber plastic bottles stored at room temperature.

1. Cober MP, Johnson CE. Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. *Am J Health-Syst Pharm* 2007; **64:** 644–6.

Dependence and Withdrawal

As for the barbiturates (see Amobarbital, p.962).

Adverse Effects

The most frequent adverse effect associated with phenobarbital is sedation, but this often becomes less marked with continued use. Like some of the other antiepileptics, phenobarbital may produce subtle mood changes and impairment of cognition and memory that may not be apparent without testing. Depression may occur.

Prolonged use can occasionally result in folate deficiency; rarely, megaloblastic anaemia has been reported. There is some evidence that phenobarbital interferes with vitamin D metabolism.

At high doses nystagmus and ataxia may occur and the typical barbiturate-induced respiratory depression may become severe. Overdosage can prove fatal; toxic effects include coma, severe respiratory and cardiovascular depression, with hypotension and shock leading to renal failure. Hypothermia may occur, with associated pyrexia during recovery. Skin blisters (bullae) reportedly occur in about 6% of patients with barbiturate overdose.

Sodium salts of barbiturates have a very high pH in solution, and necrosis has followed subcutaneous injection or extravasation. Intravenous injections can be hazardous and cause hypotension, shock, laryngospasm, and apnoea, especially if given too rapidly.

Hypersensitivity reactions occur in a small proportion of patients; skin reactions are reported in 1 to 3% of patients taking phenobarbital, and are most commonly maculopapular, morbilliform, or scarlatiniform rashes. More severe reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are extremely rare. Hepatitis and disturbances of liver function have been reported.

Paradoxical excitement, restlessness, and confusion may sometimes occur in the elderly, and irritability and hyperactivity may occur in children.

Neonatal drug dependence and symptoms resembling vitamin K deficiency have been reported in infants born to mothers who received phenobarbital during pregnancy. Congenital malformations have been reported in children of women who received phenobarbital during pregnancy but the causal role of the drug is a matter of some debate.

Effects on the blood. For the effects of antiepileptics including phenobarbital on serum folate, see under Phenytoin, p.495.

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

Effects on connective tissue. The use of phenobarbital and primidone has been associated with the development of Dupuytren's contracture, frozen shoulder, Ledderhose's syndrome, Peyronie's disease, fibromas, and general joint pain.[1]

1. Mattson RH, *et al.* Barbiturate-related connective tissue disorders. *Arch Intern Med* 1989; **149:** 911–14.

Effects on the endocrine system. For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p.496.

Barbiturates may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p.2172.

Effects on the liver. For mention of the effects of phenobarbital on the liver, see under Phenytoin, p.496.

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

DEPRESSION. Follow-up of 28 patients aged 6 to 16 who had received phenobarbital or carbamazepine for epilepsy indicated that the rate of major depression was significantly higher in those receiving phenobarbital.[1] It was recommended that treatment with phenobarbital should be avoided particularly in patients with a personal or family history of an affective disorder; patients who do receive it should be monitored for symptoms of depression.

1. Brent DA, *et al.* Phenobarbital treatment and major depressive disorder in children with epilepsy: a naturalistic follow-up. *Pediatrics* 1990; **85:** 1086–91.

DISTURBED BEHAVIOUR. Disturbed behaviour is a recognised adverse effect of phenobarbital, especially in children and the elderly; however, no excess in behavioural adverse effects was seen[1] on follow-up for up to 12 months in 40 children who took phenobarbital when compared with 45 who took carbamazepine.

1. Banu SH, *et al.* Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial. Abridged version: *BMJ* 2007; **334:** 1207–10. Full version: http://www.bmj.com/cgi/reprint/334/7605/1207 (accessed 09/06/08)

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some antiepileptics including phenobarbital.[1,2] Some have estimated the incidence at 1 in 1000 to 1 in 10 000