8. Bratton SL, *et al.* Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, and Joint Section on Neuotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury—XIII: antiseizure prophylaxis. *J Neurotrauma* 2007; **24** (suppl 1): S-83–S-86. Also available at: http://www.braintrauma.org/site/DocServer/Management_3rd_Edition.pdf?docID=222 (accessed 01/09/08)
9. Stowe CD, *et al.* Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. *J Clin Pharmacol* 2000; **40:** 1452–61.

Status epilepticus. A benzodiazepine is the usual choice to abort an attack of status epilepticus (p.469). If this fails to control the seizures or the seizures recur, then intravenous phenytoin may be given.

Once seizures have been brought under control, maintenance antiepileptic therapy may be started.

Syndrome of inappropriate ADH secretion. Phenytoin has been used occasionally to inhibit pituitary antidiuretic hormone (ADH) secretion in patients with the syndrome of inappropriate ADH secretion (SIADH), the management of which is discussed on p.2182.

Tinnitus. Phenytoin is one of many drugs that have been tried in tinnitus (p.1866), but although it has been reported to be effective in some patients it is rarely used because of problems with adverse effects.

Withdrawal syndromes. Phenytoin has little place in the management of seizures associated with the *alcohol withdrawal syndrome* (p.1626). Prophylaxis with phenytoin has been shown[1,2] to be ineffective for prevention of recurrent alcohol-related seizures and therefore drugs such as the benzodiazepines or clomethiazole, which are effective both for the treatment and prophylaxis of such seizures, are preferred.

Results from a double-blind study[3] indicated that phenytoin was associated with a reduction in *cocaine abuse* compared with placebo. The abuse of cocaine is discussed on p.1858 and treatment of cocaine withdrawal on p.1860.

1. Chance JF. Emergency department treatment of alcohol withdrawal seizures with phenytoin. *Ann Emerg Med* 1991; **20:** 520–2.
2. Rathlev NK, *et al.* The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. *Ann Emerg Med* 1994; **23:** 513–8.
3. Crosby RD, *et al.* Phenytoin in the treatment of cocaine abuse: a double-blind study. *Clin Pharmacol Ther* 1996; **59:** 458–68.

Wounds and ulcers. Phenytoin has been used to promote wound healing (p.1585). Topical application of phenytoin has produced encouraging results in the healing of various types of ulcers[1-7] and large abscess cavities.[8] It has been suggested that phenytoin may reduce bacterial colonisation by changing the pH or by a direct antibacterial effect.[2] The enhanced wound healing may also be due to increased fibroblast proliferation and increased collagen content.[2] Limited absorption from the wound site may occur[9,10] and patients may need to be monitored for signs of toxicity. A systematic review,[11] which included some of these studies, found evidence to support the use of phenytoin in the treatment of leg ulcers, leprosy wounds, chronic wounds, and diabetic foot ulcers despite the poor methodological quality in the majority of studies.

1. Muthukumarasamy MG, *et al.* Topical phenytoin in diabetic foot ulcers. *Diabetes Care* 1991; **14:** 909–11.
2. Pendse AK, *et al.* Topical phenytoin in wound healing. *Int J Dermatol* 1993; **32:** 214–17.
3. Anstead GM, *et al.* Phenytoin in wound healing. *Ann Pharmacother* 1996; **30:** 768–75.
4. Adjei O, *et al.* Phenytoin in the treatment of Buruli ulcer. *Trans R Soc Trop Med Hyg* 1998; **92:** 108–9.
5. Rhodes RS, *et al.* Topical phenytoin treatment of stage II decubitus ulcers in the elderly. *Ann Pharmacother* 2001; **35:** 675–81.
6. Bhatia A, *et al.* Topical phenytoin suspension and normal saline in the treatment of leprosy trophic ulcers: a randomized, double-blind, comparative study. *J Dermatolog Treat* 2004; **15:** 321–7.
7. Younes N, *et al.* Wound bed preparation with 10 percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. *Dermatol Online J* 2006; **12:** 5. Available at: http://dermatology.cdlib.org/126/pearls/phenytoin/younes.html (accessed 09/06/08)
8. Lodha SC, *et al.* Role of phenytoin in healing of large abscess cavities. *Br J Surg* 1991; **78:** 105–8.
9. Gore R, *et al.* Topical phenytoin. *Pharm J* 1991; **247:** 620.
10. Lewis WG, Rhodes RS. Systemic absorption of topical phenytoin sodium. *Ann Pharmacother* 1994; **28:** 961.
11. Shaw J, *et al.* The clinical effect of topical phenytoin on wound healing: a systematic review. *Br J Dermatol* 2007; **157:** 997–1004.

Preparations

BP 2008: Phenytoin Capsules; Phenytoin Injection; Phenytoin Oral Suspension; Phenytoin Tablets;
USP 31: Extended Phenytoin Sodium Capsules; Phenytoin Oral Suspension; Phenytoin Sodium Injection; Phenytoin Tablets; Prompt Phenytoin Sodium Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Epamin; Etoina; Fenigramon; Fenitenk; Lotoquis Simple; Opliphon; ***Austral.:*** Dilantin; ***Austria:*** Epanutin; Epilan-D; Phenhydan; ***Belg.:*** Diphantoine; Epanutin; ***Braz.:*** Dantalin; Epelin; Fenital; Feniton; Hidantal; Unifenitoin; ***Canad.:*** Dilantin; ***Chile:*** Epamin; ***Cz.:*** Epanutin; Epilan-D; Phenhydan†; Sodanton†; ***Fin.:*** Hydantin; ***Fr.:*** Di-Hydan; Dilantin; ***Ger.:*** Epanutin†; Phenhydan; ***Gr.:*** Epanutin; ***Hong Kong:*** Dilantin; Ditoin; ***Hung.:*** Diphedan; Epanutin; ***India:*** Dilantin; Epsolin; Eptoin; ***Indon.:*** Dilantin; Ikaphen; Kutoin; Movileps; Phenilep; ***Irl.:*** Epanutin; ***Israel:*** Dilantin; Epanutin; ***Ital.:*** Aurantin; Dintoina; ***Malaysia:*** Dilantin; Ditoin; ***Mex.:*** Biodan; Comvufen; Epamin; Fenidantoin S; Feniffler; Fenitron; Hidantoina; Nuctane†; ***Neth.:*** Diphantoine; Epanutin; ***Norw.:*** Epinat; ***NZ:*** Dilantin; ***Philipp.:*** Dilantin; Epilantin; ***Pol.:*** Epanutin; ***Port.:*** Fenitan; Hidantina; ***S.Afr.:*** Epanutin; ***Singapore:*** Dilantin; ***Spain:*** Epanutin; Neosidantoina; Sinergina; ***Swed.:*** Epanutin; Fenantoin; Lehydan; ***Switz.:*** Epanutin†; Epilantine†; Phenhydan; ***Thai.:*** Dilantin; Ditoin; Ditomed; Pepsytoin; Utoin; ***Turk.:*** Epanutin; Epdantoin; Hidantin; Phenydan; ***UK:*** Epanutin; ***USA:*** Dilantin; Phenytek; ***Venez.:*** Dantoinal; Dilantin; Epamin; Fentoinal.

Multi-ingredient: ***Arg.:*** Cumatil L; Lotoquis; ***Belg.:*** Vethoine; ***Braz.:*** Dialudon; Gamibetal Complex†; Taludon†; ***Cz.:*** Sanepil; ***Gr.:*** Diphenal; ***India:*** Dilantin with Phenobarbital; Epilan; Garoin; ***Indon.:*** Ditalin; ***Ital.:*** Dintoinale; Gamibetal Complex; Metinal-Idantoina; Metinal-Idantoina L; ***Mex.:*** Alepsal Compuesto; Gamibetal Complex; ***Port.:*** Hidantina Composta†; ***Spain:*** Epilantin†; Equidan†; Redutona.

Pregabalin *(BAN, USAN, rINN)*

CI-1008; PD-144723; Pregabalina; Prégabaline; Pregabalinum.
(*S*)-3-(Aminomethyl)-5-methylhexanoic acid.

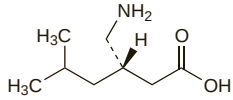
Прегабалин

$C_8H_{17}NO_2$ = 159.2.

CAS — 148553-50-8.

ATC — N03AX16.

ATC Vet — QN03AX16.



Adverse Effects and Precautions

The most common adverse effects reported during therapy with pregabalin are dizziness and somnolence. Other common adverse effects include blurred vision, diplopia, increased appetite and weight gain, dry mouth, constipation, vomiting, flatulence, euphoria, confusion, reduced libido, erectile dysfunction, irritability, vertigo, ataxia, tremor, dysarthria, paraesthesia, fatigue, and oedema. Disturbances of attention, memory, coordination, and gait also occur frequently. Syncope and congestive heart failure have been reported less frequently. Reversible renal failure, elevation of creatine kinase concentration, and rhabdomyolysis have been reported rarely. Hypersensitivity reactions have occurred shortly after starting pregabalin therapy; symptoms include rash, blisters, urticaria, dyspnoea, and wheezing. Stevens-Johnson syndrome has also been reported. An increased incidence of haemangiosarcoma was observed in *mice* that had been given high doses of pregabalin.

Licensed product information states that care is required when withdrawing pregabalin therapy, regardless of the indication—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 mental function. For a review of the effects of antiepileptic therapy on *cognition,* and the effects of pregabalin on *mood* (including the risk of suicidal ideation), see p.468.

Hypersensitivity reactions. The Australian Adverse Drug Reactions Advisory Committee[1] stated in December 2007 that 13% of all pregabalin adverse reaction reports in its database were hypersensitivity reactions. Presenting symptoms included anaphylaxis, skin rash, and angioedema. Of the 22 reports received, 6 women developed symptoms within hours of their first dose and pregabalin was the sole suspected drug in 14.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Reports of hypersensitivity reactions to pregabalin. *Aust Adverse Drug React Bull* 2007; **26:** 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0712.pdf (accessed 09/06/08)

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

Pharmacokinetics

Pregabalin is rapidly absorbed after oral doses and peak plasma concentrations are achieved within 1.5 hours. Oral bioavailability is about 90%. The rate but not the extent of absorption is reduced if given with food but this is not clinically significant. Steady state is achieved after 1 to 2 days. Pregabalin is not bound to plasma proteins and undergoes negligible metabolism. About 98% of a dose is excreted in the urine as unchanged drug. The mean elimination half-life is 6.3 hours. Pregabalin is removed by haemodialysis.

Distribution into milk has been found in studies in *rats*.

Renal impairment. References.

1. Randinitis EJ, *et al.* Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol* 2003; **43:** 277–83.

Uses and Administration

Pregabalin is an antiepileptic used as an adjunct in the treatment of partial seizures with or without secondary generalisation. It is also used in the treatment of generalised anxiety disorder, neuropathic pain, and fibromyalgia.

Pregabalin is given orally in 2 or 3 divided doses daily.

The initial dose in the treatment of **epilepsy** is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 600 mg daily after another week.

In the treatment of **generalised anxiety disorder**, the initial dose is 150 mg daily; this may be increased at weekly intervals in steps of 150 mg, to a maximum of 600 mg daily.

For **neuropathic pain** the initial dose in the UK is 150 mg daily increased after 3 to 7 days according to response to 300 mg daily and then to 600 mg daily after another 7 days. Similar doses are licensed in the USA for the treatment of neuropathic pain in diabetic neuropathy and postherpetic neuralgia, although a maximum daily dose of 300 mg is recommended in diabetic neuropathy.

For **fibromyalgia** the initial dose is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 450 mg daily if necessary.

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

As with other antiepileptics, withdrawal of pregabalin therapy in epilepsy 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 states that if pregabalin therapy has to be stopped, this should be done gradually over a minimum of 1 week, regardless of indication.

◊ References.

1. Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacother* 2005; **39:** 2029–37.
2. Tassone DM, *et al.* Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther* 2007; **29:** 26–48.

Administration in renal impairment. The dose of pregabalin for patients with renal impairment should be reduced according to creatinine clearance (CC):

- CC 30 to less than 60 mL/minute: starting daily dose: 75 mg; maximum daily dose: 300 mg; daily dose given in 2 or 3 divided doses
- CC 15 to less than 30 mL/minute: starting daily dose: 25 to 50 mg; maximum daily dose: 150 mg; daily dose given in 2 divided doses or once daily
- CC less than 15 mL/minute: starting daily dose: 25 mg; maximum daily dose: 75 mg; daily dose given as one dose
- haemodialysis patients should receive in addition to the daily dose a supplementary dose of 25 to 100 mg immediately after each 4-hour haemodialysis session

Anxiety disorders. Pregabalin is used for the treatment of generalised anxiety disorder (p.952); it has also been tried in social anxiety disorder (see Phobic Disorders, p.953).

References.

1. Pande AC, *et al.* Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry* 2003; **160:** 533–40.
2. Feltner DE, *et al.* A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol* 2003; **23:** 240–9.
3. Pande AC, *et al.* Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2004; **24:** 141–9.
4. Rickels K, *et al.* Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. *Arch Gen Psychiatry* 2005; **62:** 1022–30.
5. Owen RT. Pregabalin: its efficacy, safety and tolerability profile in generalized anxiety. *Drugs Today* 2007; **43:** 601–10.

Epilepsy. Pregabalin is one of the newer drugs used as adjunctive therapy in patients with partial seizures with or without secondary generalisation (p.465). It appears to be reasonably well tolerated.

References.

1. Miller R, *et al.* Exposure-response analysis of pregabalin add-on treatment of patients with refractory partial seizures. *Clin Pharmacol Ther* 2003; **73:** 491–505.
2. Arroyo S, *et al.* Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. *Epilepsia* 2004; **45:** 20–7.
3. Elger CE, *et al.* Pregabalin add-on treatment in patients with partial seizures: a novel evaluation of flexible-dose and fixed-dose treatment in a double-blind, placebo-controlled study. *Epilepsia* 2005; **46:** 1926–36.
4. Hamandi K, Sander JW. Pregabalin: a new antiepileptic drug for refractory epilepsy. *Seizure* 2006; **15:** 73–8.
5. Lozsadi D, *et al.* Pregabalin add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/06/08).

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p.2). Although carbamazepine appears to be the antiepileptic most frequently used, pregabalin is also given in the treatment of peripheral neuropathic pain[1] including postherpetic neuralgia[2,3] (p.9) and painful diabetic neuropathy[4,5] (p.6). Pregabalin may also be used in central neuropathic pain[6,7] (p.6).

1. Blommel ML, Blommel AL. Pregabalin: an antiepileptic agent useful for neuropathic pain. *Am J Health-Syst Pharm* 2007; **64:** 1475–82.
2. Sabatowski R, *et al.* Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain* 2004; **109:** 26–35.
3. Frampton JE, Foster RH. Pregabalin: in the treatment of postherpetic neuralgia. *Drugs* 2005; **65:** 111–18.
4. Rosenstock J, *et al.* Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain* 2004; **110:** 628–38.
5. Frampton JE, Scott LJ. Pregabalin: in the treatment of painful diabetic peripheral neuropathy. *Drugs* 2004; **64:** 2813–20.
6. Siddall PJ, *et al.* Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* 2006; **67:** 1792–800.
7. Vranken JH, *et al.* Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 2008; **136:** 150–7.

Postoperative pain. There is growing interest in the use of analgesic adjuvants including antiepileptics such as pregabalin to modulate opioid dosage and efficacy for postoperative pain (see p.4).

References.

1. Dahl JB, *et al.* 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; **48:** 1130–6.
2. Tiippana EM, *et al.* Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007; **104:** 1545–56.

Soft-tissue rheumatism. Three large, multicentre controlled studies[1-3] have shown that pregabalin in oral doses of between 300 and 600 mg daily is effective in reducing pain and other core symptoms of fibromyalgia (see Soft-tissue Rheumatism, p.13) such as sleep disturbance and fatigue. The drug was reported to be generally well tolerated, dizziness and somnolence being the most common adverse effects. Pain relief appears to be largely independent of reduction in anxiety or depression scores.[4]

1. Crofford LJ, *et al.* Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 1264–73.
2. Mease PJ, *et al.* A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol* 2008; **35:** 502–14.
3. Crofford LJ, *et al.* Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain* 2008; **136:** 419–31.
4. Arnold LM, *et al.* The effect of anxiety and depression on improvements in pain in a randomized, controlled trial of pregabalin for treatment of fibromyalgia. *Pain Med* 2007; **8:** 633–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Lyrica; ***Austral.:*** Lyrica; ***Belg.:*** Lyrica; ***Canad.:*** Lyrica; ***Chile:*** Lyrica; Pregobin; ***Cz.:*** Lyrica; ***Denm.:*** Lyrica; ***Fin.:*** Lyrica; ***Fr.:*** Lyrica; ***Ger.:*** Lyrica; ***Gr.:*** Lyrica; ***Hong Kong:*** Lyrica; ***Hung.:*** Lyrica; ***India:*** Pregab; ***Indon.:*** Lyrica; ***Irl.:*** Lyrica; ***Ital.:*** Lyrica; ***Mex.:*** Lyrica; ***Neth.:*** Lyrica; ***Norw.:*** Lyrica; ***NZ:*** Lyrica; ***Philipp.:*** Lyrica; ***Pol.:*** Lyrica; ***Port.:*** Lyrica; ***Rus.:*** Lyrica (Лирика); ***Singapore:*** Lyrica; ***Spain:*** Lyrica; ***Swed.:*** Lyrica; ***Switz.:*** Lyrica; ***UK:*** Lyrica; ***USA:*** Lyrica; ***Venez.:*** Lyrica.

Primidone *(BAN, rINN)*

Desoxifenobarbitona; Hexamidinum; Primaclona; Primaclone; Primidon; Primidona; Primidonas; Primidoni; Primidonum; Prymidon. 5-Ethyl-5-phenylperhydropyrimidine-4,6-dione.

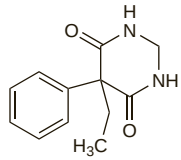
Примидон

$C_{12}H_{14}N_2O_2$ = 218.3.

CAS — 125-33-7.

ATC — N03AA03.

ATC Vet — QN03AA03.



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

Ph. Eur. 6.2 (Primidone). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in alkaline solutions.

USP 31 (Primidone). A white, odourless, crystalline powder. Soluble 1 in 2000 of water and 1 in 200 of alcohol; very slightly soluble in most organic solvents.

Adverse Effects, Treatment, and Precautions

As for Phenobarbital, p.492.

Adverse effects may be more frequent than with phenobarbital. Most patients rapidly develop tolerance to the adverse effects of primidone, including ataxia, dizziness, drowsiness, headache, nausea and vomiting, nystagmus, skin rashes, and visual disturbances.

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

Effects on the blood. For a report of delayed agranulocytosis in a patient treated with phenytoin and primidone, see p.495.

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

Overdosage. Crystalluria has been reported[1] after acute overdosage of primidone and 7 other reported cases were also reviewed. Based on these few reports, crystalluria appears to be associated with serum-primidone concentrations in excess of 80 micrograms/mL. There is evidence from 2 reports of renal damage associated with crystal formation *in vivo*. Vigorous hydration is recommended in patients at risk, in order to lessen the potential for renal toxicity and improve elimination.

1. Lehmann DF. Primidone crystalluria following overdose: a report of a case and an analysis of the literature. *Med Toxicol* 1987; **2:** 383–7.

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

Tremor. It was noted that patients receiving primidone for essential tremor have a high incidence of acute adverse reactions after small initial doses.[1] This could be due to the absence of induced hepatic enzymes in these patients previously not exposed to antiepileptics.

1. Findley LJ, *et al.* Primidone in essential tremor of the hands and head: a double blind controlled clinical study. *J Neurol Neurosurg Psychiatry* 1985; **48:** 911–15.

Interactions

Primidone is metabolised in the body in part to phenobarbital, and interactions recorded for phenobarbital (p.493) might potentially occur in patients receiving primidone. In addition, enzyme-inducing drugs enhance this metabolism and have the potential to produce elevated phenobarbital concentrations.

Antiepileptics. Both *phenytoin*[1] and *carbamazepine*[2] have been reported to enhance the metabolism of primidone to phenobarbital and when primidone was combined with phenytoin there have been instances of phenobarbital toxicity.[3] *Vigabatrin* has been reported[4] to lower plasma concentrations of primidone in some patients, although it is unlikely that dosage changes would be necessary. *Valproate* may increase plasma concentrations of primidone and phenobarbital, but patient response seems to be inconsistent.[5-7]

1. Reynolds EH, *et al.* Interaction of phenytoin and primidone. *BMJ* 1975; **2:** 594–5.
2. Baciewicz AM. Carbamazepine drug interactions. *Ther Drug Monit* 1986; **8:** 305–17.
3. Galdames D, *et al.* Interacción fenitoína-primidona: intoxicación por fenobarbital, en un adulto tratado con ambas drogas. *Rev Med Chil* 1980; **108:** 716–20.
4. Browne TR, *et al.* A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* 1989; **27** (suppl 1): 95S–100S.
5. Windorfer A, *et al.* Elevation of diphenylhydantoin and primidone serum concentration by addition of dipropylacetate, a new anticonvulsant drug. *Acta Paediatr Scand* 1975; **64:** 271–2.
6. Bruni J. Valproic acid and plasma levels of primidone and derived phenobarbital. *Can J Neurol Sci* 1981; **8:** 91–2.
7. Yukawa E, *et al.* The effect of concurrent administration of sodium valproate on serum levels of primidone and its metabolite phenobarbital. *J Clin Pharm Ther* 1989; **14:** 387–92.

Pharmacokinetics

Primidone is readily absorbed from the gastrointestinal tract and is reported to have a plasma half-life ranging from 10 to 15 hours, which is shorter than those of its principal metabolites phenylethylmalonamide and phenobarbital, both of which are active. Therapeutic plasma concentrations of primidone have been suggested to be between 5 and 12 micrograms/mL. It is excreted in urine as unchanged drug (40%) and metabolites.

Primidone is widely distributed but is only partially bound to plasma proteins; it has been suggested that it exhibits variable binding of up to about 20%. It crosses the placenta and is distributed into breast milk.

The pharmacokinetics of primidone may be affected by use with other antiepileptics (see under Interactions, above).

Uses and Administration

Primidone is an antiepileptic that is partially metabolised to phenobarbital (p.494), but is also considered to have some antiepileptic activity in its own right. It may be given to control partial and generalised tonic-clonic seizures. Primidone is also used in the management of essential tremor.

In the treatment of **epilepsy** the dose of primidone should be adjusted according to response; a limited correlation with plasma concentrations has suggested that concentrations of 5 to 12 micrograms/mL (23 to 55 micromoles/litre) are usually necessary, but the *BNF* recommends monitoring of phenobarbital concentrations instead.

Recommended initial oral doses in the UK are 125 mg at bedtime increased, if necessary, by 125 mg every 3 days to a total of 500 mg daily given in 2 divided doses. If necessary, the daily dose may be increased further every 3 days by 250 mg up to a maximum of 1.5 g daily given in divided doses. Usual maintenance doses are 0.75 to 1.5 g daily; maintenance doses are usually given as 2 divided doses. Dosage recommendations in the USA are generally similar although a maximum daily dose of 2 g is permitted.

For doses in children, see below.

As with other antiepileptics, withdrawal of primidone 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.

For **essential tremor** primidone is usually started at daily oral doses of 50 mg as the syrup or 62.5 mg as the tablet, increased gradually over 2 to 3 weeks if necessary, to a maximum of 750 mg daily.

Administration in children. Children may be given primidone to control partial and generalised tonic-clonic seizures. Recommended initial oral doses in the UK are 125 mg at bedtime, increased if necessary, by 125 mg every 3 days to the following usual maintenance daily doses (given in 2 divided doses) according to age:

- up to 2 years: 250 to 500 mg
- 2 to 5 years: 500 to 750 mg
- 6 to 9 years: 750 to 1000 mg

Children aged over 9 years may be given the usual adult dose (see above).

In the USA, a lower initial oral dose of 50 mg daily is recommended. This is doubled every 3 days, to reach a usual maintenance dose of 125 to 250 mg 3 times daily (10 to 25 mg/kg daily in divided doses) after 10 or more days. Children over 8 years of age may be given the usual adult dose as above.

Epilepsy. Primidone, like its metabolite phenobarbital, is used in the treatment of epilepsy (p.465) for partial seizures with or