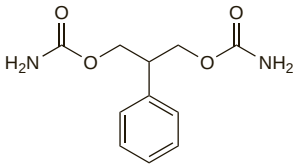
Felbamate *(USAN, rINN)*

AD-03055; Felbamato; Felbamatum; W-554. 2-Phenyl-1,3-propanediol dicarbamate.

Фелбамат

$C_{11}H_{14}N_2O_4$ = 238.2.
CAS — 25451-15-4.
ATC — N03AX10.
ATC Vet — QN03AX10.



Adverse Effects

The most frequently reported adverse effects with felbamate are anorexia, weight loss, nausea and vomiting, rash, insomnia, headache, dizziness, somnolence, and diplopia. Aplastic anaemia or acute liver failure, sometimes fatal, have occurred rarely, and there have been reports of Stevens-Johnson syndrome.

Effects on the kidneys. A 15-year-old boy receiving up to 3 g of felbamate daily developed urethral obstruction due to formation of urethral stones composed of felbamate.[1] Records revealed that unidentified urinary crystals had been found in the patient's urine 2 years before presentation with acute urolithiasis.

For reports of crystalluria associated with felbamate overdosage, see below.

1. Sparagana SP, *et al.* Felbamate urolithiasis. *Epilepsia* 2001; **42:** 682–5.

Effects on mental function. For the effects of antiepileptic therapy on cognition and mood, including the risk of suicidal ideation, see p.468

Effects on the skin. Toxic epidermal necrolysis has been reported[1] in a patient 16 days after she started monotherapy with felbamate for partial complex seizures.

1. Travaglini MT, *et al.* Toxic epidermal necrolysis after initiation of felbamate therapy. *Pharmacotherapy* 1995; **15:** 260–4.

Overdosage. A 20-year-old woman presented with slurred speech and nausea 4 hours after ingesting 18 g of felbamate and 12 to 25 g of sodium valproate.[1] Over the next 4 to 5 hours she became combative, uncooperative, and progressively obtunded and eventually required endotracheal intubation and assisted ventilation. Peak plasma concentrations of 200 micrograms/mL for felbamate and 470 micrograms/mL for sodium valproate occurred 12 and 14 hours respectively after ingestion. Large quantities of macroscopic crystals, identified as containing felbamate, were noted in the urine 18 hours after ingestion and the patient developed renal failure. The crystalluria and renal failure responded to parenteral hydration. In another case report,[2] a 3-year-old child ingested 232 mg/kg of felbamate resulting in ataxia, vomiting, crystalluria, haematuria, and mild tachycardia. The plasma concentration of felbamate 15 hours after ingestion was 138 micrograms/mL. She was successfully treated with an infusion of sodium chloride 0.9% and intravenous metoclopramide; no renal impairment was seen.

1. Rengstorff DS, *et al.* Felbamate overdose complicated by massive crystalluria and acute renal failure. *J Toxicol Clin Toxicol* 2000; **38:** 667–9.
2. Meier KH, *et al.* Acute felbamate overdose with crystalluria. *Clin Toxicol* 2005; **43:** 189–92.

Precautions

Felbamate is contra-indicated in patients with a history of blood disorders or hepatic impairment. It should be used only in the treatment of severe epilepsy refractory to other antiepileptics because of the risk of fatal aplastic anaemia or acute liver failure. Patients or their carers should be advised of the symptoms of aplastic anaemia and be told to report immediately should any such symptoms develop. Complete blood counts should be carried out before the patient starts treatment and regularly during treatment (but see Epilepsy, under Uses and Administration, below). Aplastic anaemia may occur after felbamate has been stopped so patients should continue to be monitored for some time. Liver function tests are also recommended before starting and regularly (at 1- to 2-week intervals) during treatment. Felbamate should be stopped if there is any evidence of bone marrow depression or liver abnormalities.

Felbamate should be used with caution in patients with renal impairment. Felbamate may cause photosensitivity reactions and patients should be advised to take protective measures against exposure to UV radiation.

Care is required when withdrawing felbamate 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.

The elderly. Felbamate may need to be given with care in elderly patients (see Administration in the Elderly, below).

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. The metabolism of felbamate is enhanced by enzyme inducers such as phenytoin, phenobarbital, or carbamazepine. In contrast, the half-life of felbamate may be prolonged by gabapentin. Felbamate inhibits or enhances the metabolism of several other antiepileptics and care is required when it is added to therapy.

Anticoagulants. For the effect of felbamate on *warfarin*, see p.1429.

Antiepileptics. For some references to the effect of felbamate on other antiepileptics, see under *Carbamazepine*, p.474, *Phenobarbital*, p.493, *Phenytoin*, p.498, and *Valproate* p.511.

Sex hormones. For the effect of felbamate on *oral contraceptives* see p.2068 and also under Gestodene, p.2105.

Pharmacokinetics

Felbamate is well absorbed from the gastrointestinal tract and peak plasma concentrations have been reported 1 to 6 hours after oral doses. Protein binding is reported to be about 22 to 25%. It is partly metabolised in the liver by hydroxylation and conjugation to inactive metabolites. Felbamate is excreted mainly in the urine as metabolites and unchanged drug (40 to 50%); less than 5% appears in the faeces. The terminal half-life is reported to be between 16 and 23 hours. Felbamate is distributed into breast milk.

The pharmacokinetics of felbamate are reported to be linear at the doses used clinically. Therapeutic plasma concentrations have been reported to be between 30 and 80 micrograms/mL.

The pharmacokinetics of felbamate are affected by use with other antiepileptics (see Interactions, above).

◊ See under Uses and Administration (below) for mention of pharmacokinetic studies of felbamate in the elderly and in patients with renal impairment.

Uses and Administration

Felbamate is a carbamate structurally related to meprobamate (p.1006). It is used in the treatment of epilepsy (see below); however, because of its toxicity, it should only be used in severe cases unresponsive to other drugs.

Felbamate is given orally as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation. It is used in children as adjunctive therapy in controlling the seizures associated with the Lennox-Gastaut syndrome (see below).

The initial dose of felbamate when given as *monotherapy* is 1.2 g daily in 3 or 4 divided doses. The daily dose should be increased gradually under close supervision; increments of 600 mg every 2 weeks are given according to response, up to 2.4 g daily. Thereafter doses may be further increased to a maximum of 3.6 g daily if necessary.

Similar initial doses are given as *adjunctive* therapy, but the doses of the other antiepileptics should be decreased as necessary. This adjunctive dose may be increased by 1.2 g at weekly intervals, up to a maximum of 3.6 g.

As with other antiepileptics, withdrawal of felbamate 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.

◊ References.

1. Pellock JM, *et al.* Felbamate: consensus of current clinical experience. *Epilepsy Res* 2006; **71:** 89–101.

Administration in children. As an adjunct in Lennox-Gastaut syndrome, the initial oral dose of felbamate in children aged 2 to 14 years is 15 mg/kg daily in 3 to 4 divided doses. This may be increased gradually in increments of 15 mg/kg at weekly intervals to a maximum of 45 mg/kg daily; the doses of other antiepileptics should be decreased as necessary.

Those aged 14 years and over may be given the usual adult dose (see above) as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation.

Administration in the elderly. The elderly may require lower initial doses of felbamate and slower dose titration. After single doses of felbamate, plasma concentrations and half-lives were greater and mean clearance lower in elderly than in young subjects, whereas pharmacokinetic parameters after multiple dosing schedules were similar.[1]

1. Richens A, *et al.* Single and multiple dose pharmacokinetics of felbamate in the elderly. *Br J Clin Pharmacol* 1997; **44:** 129–34.

Administration in renal impairment. A single-dose pharmacokinetic study[1] indicated that in patients with renal impairment the initial dose of felbamate may need to be lower and increases made more cautiously than in patients with normal renal function (licensed product information suggests halving initial and maintenance doses).

1. Glue P, *et al.* Single-dose pharmacokinetics of felbamate in patients with renal dysfunction. *Br J Clin Pharmacol* 1997; **44:** 91–3.

Epilepsy. Although felbamate was well tolerated in clinical studies, rare but serious adverse effects were noted during early postmarketing use.[1,2] Aplastic anaemia and serious hepatotoxic reactions, sometimes with fatal outcomes, developed in some patients. Patients taking felbamate should have frequent blood counts and monitoring of liver enzymes. However there is no evidence that such monitoring will prevent adverse outcomes; in addition, the risk of aplastic anaemia is thought to decrease after the first year of therapy, and the need for ongoing blood counts is still less clear.[3] Even if detected early, aplastic anaemia and hepatic impairment may not be reversible.[1] Usage in the USA is restricted to patients with refractory partial seizures with or without secondary generalisation or for adjunctive therapy for children with Lennox-Gastaut syndrome. Guidelines on appropriate use have been issued.[3]

The overall management of epilepsy is discussed on p.465.

1. Dichter MA, Brodie MJ. New antiepileptic drugs. *N Engl J Med* 1996; **334:** 1583–90.
2. Appleton RE. The new antiepileptic drugs. *Arch Dis Child* 1996; **75:** 256–62.
3. French J, *et al.* The use of felbamate in the treatment of patients with intractable epilepsy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 1999; **40:** 803–8. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/119061174/PDFSTART (accessed 01/09/08)

Preparations

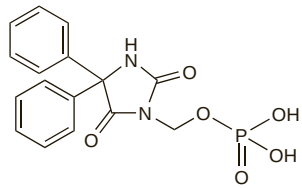
Proprietary Preparations (details are given in Part 3)
Arg.: Felbamyl; ***Austria:*** Taloxa; ***Belg.:*** Taloxa; ***Cz.:*** Taloxa†; ***Fr.:*** Taloxa; ***Ger.:*** Taloxa; ***Hung.:*** Taloxa; ***Ital.:*** Taloxa; ***Neth.:*** Taloxa; ***Norw.:*** Taloxa; ***Port.:*** Taloxa; ***Swed.:*** Taloxa; ***Switz.:*** Taloxa; ***USA:*** Felbatol.

Fosphenytoin Sodium *(BANM, USAN, rINNM)*

ACC-9653; ACC-9653-010; CI-982 (fosphenytoin or fosphenytoin sodium); Fosfenitoin Sodyum; Fosfenitoína sódica; Fosphénytoïne Sodique; Natrii Fosphenytoinum; PD-135711-15B. 5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium; 3-(Hydroxymethyl)-5,5-diphenylhydantoin disodium phosphate; 2,5-Dioxo-4,4-diphenylimidazolidin-1-ylmethyl phosphate disodium.

Натрий Фосфенитоин

$C_{16}H_{13}N_2Na_2O_6P$ = 406.2.
CAS — 93390-81-9 (fosphenytoin); 92134-98-0 (fosphenytoin sodium).
ATC — N03AB05.
ATC Vet — QN03AB05.



(fosphenytoin)

Pharmacopoeias. In *US.*
USP 31 (Fosphenytoin Sodium). A white to pale yellow solid. Freely soluble in water. pH of a 7.5% solution in water is between 8.5 and 9.5. Store in airtight containers.

Stability. References.

1. Fischer JH, *et al.* Stability of fosphenytoin sodium with intravenous solutions in glass bottles, polyvinyl chloride bags, and polypropylene syringes. *Ann Pharmacother* 1997; **31**: 553–9.

Adverse Effects and Precautions

As for Phenytoin, p.495.

Severe cardiovascular reactions, sometimes fatal, have been reported after intravenous doses of fosphenytoin. Therefore, continuous monitoring of ECG, blood pressure, and respiratory function is recommended during the infusion, and the patient should be kept under observation for at least 30 minutes after the end of the infusion. Hypotension may occur with recommended doses and rates of infusion; a reduction in the infusion rate or stopping therapy may be necessary. Fosphenytoin is contra-indicated in patients with sinus bradycar-

dia, sino-atrial block, second- or third-degree AV block, or Stokes-Adams syndrome.

Burning, itching, and paraesthesia, particularly in the groin area, have also been reported after intravenous fosphenytoin; reducing the rate of, or temporarily stopping, the infusion may relieve the discomfort.

Caution should be exercised when giving fosphenytoin to patients in whom phosphate restriction is necessary. The rate of metabolism of fosphenytoin to phenytoin may be increased in patients with hepatic or renal disease, or in those with hypoalbuminaemia, and consequently there is an increased risk of adverse effects in such patients.

Effects on the cardiovascular system. The UK CSM[1] stated in May 2000 that worldwide there had been reports of 21 cases of asystole, ventricular fibrillation, or cardiac arrest associated with intravenous use of fosphenytoin. Of these, 5 cases had received doses or infusion rates greater than recommended. There had also been 34 reports of hypotension, 15 of bradycardia, and 10 of varying degrees of heart block. Most reactions had occurred within 30 minutes of the infusion. A review[2] of adverse events associated with fosphenytoin infusion received by the FDA Adverse Event Reporting System between 1997 and 2002 identified 29 of adverse cardiac events, including 10 fatalities. Of these reports, 5 were of sinus arrest, 4 of AV block, and 8 of asystole. The authors acknowledged that the majority of patients had serious confounders including renal failure, stroke, acute cardiac ischaemia or failure, overdose, or infection.

ECG changes consistent with hypocalcaemia have occurred in a patient who received 1500 mg-equivalents of phenytoin over 85 minutes as an intravenous infusion of fosphenytoin.[3] The patient had initially been normocalcaemic and it was suggested that the effect may have been due to acute inorganic phosphate toxicity.

1. Committee on Safety of Medicines/Medicines Control Agency. Fosphenytoin sodium (Pro-Epanutin): serious arrhythmias and hypotension. *Current Problems* 2000; **26:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
2. Adams BD, *et al*. Fosphenytoin may cause hemodynamically unstable bradydysrhythmias. *J Emerg Med* 2006; **30:** 75–9.
3. Keegan MT, *et al.* Hypocalcemia-like electrocardiographic changes after administration of intravenous fosphenytoin. *Mayo Clin Proc* 2002; **77:** 584–6.

Porphyria. Phenytoin is considered unsafe in porphyric patients; it would be prudent to assume that this consideration also applied to its prodrug, fosphenytoin.

Interactions

As for Phenytoin, p.497.

Pharmacokinetics

Plasma concentrations of fosphenytoin are maximal at the end of intravenous infusion and about 30 minutes after intramuscular injection. Protein binding of fosphenytoin is high (95 to 99%), mainly to albumin, and is saturable. Fosphenytoin displaces phenytoin from protein binding sites which increases the fraction of unbound phenytoin to up to 30% for about half to one hour post-infusion. Fosphenytoin is rapidly and completely hydrolysed to phenytoin with a conversion half-life of about 15 minutes; one mmol of fosphenytoin yields one mmol of phenytoin, and the same of phosphate and formate. Metabolites of phenytoin are excreted in the urine. For the pharmacokinetics of phenytoin, see p.500.

◊ References.

1. Fischer JH, *et al.* Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet* 2003; **42:** 33–58.

Uses and Administration

Fosphenytoin is a prodrug of phenytoin (p.495) used similarly as part of the emergency treatment of status epilepticus (p.469). It is also used for the prevention and treatment of post-traumatic seizures (p.501) associated with neurosurgery or head trauma and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy (p.465).

Fosphenytoin is given as the sodium salt and doses of fosphenytoin sodium are expressed as phenytoin sodium equivalents (PSE); therefore no adjustment in dosage is necessary when substituting fosphenytoin for phenytoin or vice versa. Fosphenytoin may be given by intramuscular injection or intravenous infusion; only the intravenous route is recommended in children.

The maximum rate of intravenous infusion in PSE is 150 mg/minute and should not be exceeded. Continuous monitoring of ECG, blood pressure, and respiratory function is recommended during intravenous infusion. Patients should also be observed for at least 30 minutes after the end of infusion.

In the treatment of tonic-clonic status epilepticus a benzodiazepine such as diazepam or lorazepam is usually given initially intravenously or rectally followed by fosphenytoin. In the UK, the loading dose in PSE is 15 mg/kg given as a single dose by intravenous infusion at a rate of 100 to 150 mg/minute. The intramuscular route is not appropriate for the management of status epilepticus because peak phenytoin concentrations will not be reached quickly enough. The loading dose for seizures other than in status epilepticus is 10 to 15 mg/kg given as a single dose by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Initial maintenance doses for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 or 2 divided doses by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given intramuscularly or by intravenous infusion at a rate of 50 to 100 mg/minute may be substituted for oral phenytoin at the same equivalent total daily dose for up to 5 days.

In the USA, loading doses in PSE of up to 20 mg/kg are permitted, and initial maintenance doses are 4 to 6 mg/kg daily.

For doses in children, see below.

A lower loading dose and/or infusion rate, and lower or less frequent maintenance dosing may be necessary for elderly patients; UK licensed product information suggests a reduction in dose or rate of 10 to 25%. Similar reductions are suggested for patients with renal or hepatic impairment (see also below) or in those with hypoalbuminaemia, except in the treatment of status epilepticus.

◊ References.

1. Wilder BJ, *et al.* Safety and tolerance of multiple doses of intramuscular fosphenytoin substituted for oral phenytoin in epilepsy or neurosurgery. *Arch Neurol* 1996; **53:** 764–8.
2. Meek PD, *et al.* Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. *Arch Intern Med* 1999; **159:** 2639–44.
3. Heafield MTE. Managing status epilepticus: new drug offers real advantages. *BMJ* 2000: **320:** 953–4.
4. DeToledo JC, Ramsay RE. Fosphenytoin and phenytoin in patients with status epilepticus: improved tolerability versus increased costs. *Drug Safety* 2000; **22:** 459–66.

Administration in children. In the UK, fosphenytoin sodium may be given to children over 5 years of age for the emergency treatment of status epilepticus, the prevention and treatment of post-traumatic seizures associated with neurosurgery or head trauma, and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy. It is given by intravenous infusion and doses are expressed as phenytoin sodium equivalents (PSE).

In the treatment of tonic-clonic status epilepticus, the loading dose in PSE is 15 mg/kg given as a single dose at a rate of 2 to 3 mg/kg per minute; however, the *BNFC* allows up to 20 mg/kg. In the treatment or prophylaxis of seizures other than in status epilepticus, the loading dose in PSE is 10 to 15 mg/kg given as a single dose at a rate of 1 to 2 mg/kg per minute. The maximum rate of infusion of loading doses is 3 mg/kg per minute or 150 mg/minute and should not be exceeded. Initial maintenance doses in PSE for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 to 4 divided doses at a rate of 1 to 2 mg/kg per minute, not exceeding 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given at a rate of 1 to 2 mg/kg per minute, not exceeding 50 to 100 mg/minute, may be substituted for oral phenytoin at equivalent total daily doses for up to 5 days.

Similar precautions to those in adults apply to the monitoring of clinical parameters and plasma-phenytoin concentrations in children (see above).

Administration in hepatic or renal impairment. The rate and extent of conversion of fosphenytoin to phenytoin in patients with hepatic cirrhosis or renal impairment requiring dialysis was not found to be significantly different from those for healthy controls.[1] However, there was a trend towards an increase in fosphenytoin clearance and a decrease in the time to peak phenytoin concentrations in those with hepatic or renal impairment. Consequently, the authors recommended that fosphenytoin may need to be given at lower doses or infused more slowly (see above for the licensed product recommendations).

1. Aweeka FT, *et al.* Pharmacokinetics of fosphenytoin in patients with hepatic or renal disease. *Epilepsia* 1999; **40:** 777–82.

Preparations

USP 31: Fosphenytoin Sodium Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Pro-Epanutin†; ***Austria:*** Pro-Epanutin; ***Canad.:*** Cerebyx; ***Denm.:*** Pro-Epanutin; ***Fin.:*** Pro-Epanutin; ***Fr.:*** Prodilantin; ***Gr.:*** Pro-Epanutin; ***Irl.:*** Pro-Epanutin; ***Neth.:*** Pro-Epanutin†; ***Norw.:*** Pro-Epanutin; ***Spain:*** Cereneu; ***Swed.:*** Pro-Epanutin; ***UK:*** Pro-Epanutin; ***USA:*** Cerebyx.

Gabapentin *(BAN, USAN, rINN)*

CI-945; Gabapentiini; Gabapentina; Gabapentine; Gabapentinum; GOE-3450. 1-(Aminomethyl)cyclohexaneacetic acid.

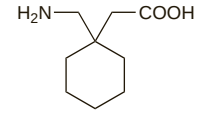
Габапентин

$C_9H_{17}NO_2$ = 171.2.

CAS — 60142-96-3.

ATC — N03AX12.

ATC Vet — QN03AX12.



Pharmacopoeias. In *US.*

USP 31 (Gabapentin). A white to off-white, crystalline solid. Freely soluble in water and in alkaline and acidic solutions. A 2% solution in water has a pH of 6.5 to 8.0.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with gabapentin are somnolence, dizziness, ataxia, and fatigue. Nystagmus, tremor, diplopia, amblyopia, pharyngitis, rhinitis, dysarthria, nausea and vomiting, weight gain, oedema, dyspepsia, amnesia, weakness, paraesthesia, arthralgia, purpura, leucopenia, anxiety, and urinary-tract infection may occur less frequently. Rarely, pancreatitis, altered liver function tests, erythema multiforme, Stevens-Johnson syndrome, myalgia, headache, and blood glucose fluctuations in diabetics have been reported. Common psychiatric effects include confusion, depression, and nervousness, and, more rarely, hallucinations and psychoses. Other adverse effects include acute renal failure, allergic reactions, alopecia, angioedema, chest pain, hepatitis, jaundice, movement disorders such as choreoathetosis, dyskinesia and dystonia, palpitations, thrombocytopenia, and tinnitus.

Gabapentin should be used with caution in patients with renal impairment and in those undergoing haemodialysis. False positive readings have been reported with some urinary protein tests in patients taking gabapentin.

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

Incidence of adverse effects. A postmarketing surveillance study[1] of 3100 patients taking gabapentin identified drowsiness or sedation as the most frequent adverse effect, occurring in about 6.7%. The incidences of other adverse effects were: headache, 3.6%; fatigue, 3.5%; nausea and vomiting, 2.6%; and dizziness, 2.4%. Less common adverse events included rash, visual defect, and ataxia. Overall, adverse effects were reported as the reason for stopping treatment in about 10% of patients. In the 136 children aged under 12 years whose data were included in the study, the most frequently reported treatment-related adverse events were eczema, rash, and vomiting. In this study, none of the 11 infants born to mothers taking gabapentin throughout pregnancy had congenital abnormalities.

1. Wilton LV, Shakir S. A postmarketing surveillance study of gabapentin as add-on therapy for 3,100 patients in England. *Epilepsia* 2002; **43:** 983–92.

Breast feeding. For mention of the pharmacokinetics of gabapentin during pregnancy and breast feeding, see under Pharmacokinetics, below.

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