other antineoplastics in the treatment of various malignancies, with some reported benefit.

1. Bug G, *et al.* Clinical trial of valproic acid and all-trans retinoic acid in patients with poor-risk acute myeloid leukemia. *Cancer* 2005; **104:** 2717–25.
2. Raffoux E, *et al.* Treatment of elderly acute myeloid leukemia with valproic acid and all-trans retinoic acid. *Haematologica* 2005; **90:** 986–8.
3. Pilatrino C, *et al.* Increase in platelet count in older, poor-risk patients with acute myeloid leukemia or myelodysplastic syndrome treated with valproic acid and all-trans retinoic acid. *Cancer* 2005; **104:** 101–9.
4. Chavez-Blanco A, *et al.* Histone acetylation and histone deacetylase activity of magnesium valproate in tumor and peripheral blood of patients with cervical cancer: a phase I study. *Mol Cancer* 2005; **4:** 22. Full version: http://www.molecular-cancer.com/content/pdf/1476-4598-4-22.pdf (accessed 09/06/08)
5. Münster P, *et al.* Phase I trial of histone deacetylase inhibition by valproic acid followed by the topoisomerase II inhibitor epirubicin in advanced solid tumors: a clinical and translational study. *J Clin Oncol* 2007; **25:** 1979–85.
6. Blum W, *et al.* Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia. *J Clin Oncol* 2007; **25:** 3884–91.

Migraine. See under Headache, above.

Muscle spasm. The mainstay of management of *spasticity* is physiotherapy and an antispastic drug (see p.1887). Valproate has been tried for its GABAergic activity and case reports[1] of 4 patients with spastic conditions of various aetiologies indicated that the addition of valproate to the existing regimen of antispastic drugs might produce improvements in spasticity and pain; further studies are warranted.

Valproate has also been tried[2] in the management of *stiff-man syndrome* (see under Muscle Spasm, p.993) unresponsive to diazepam.

1. Zachariah SB, *et al.* Positive response to oral divalproex sodium (Depakote) in patients with spasticity and pain. *Am J Med Sci* 1994; **308:** 38–40.
2. Spehlmann R, *et al.* Improvement of stiff-man syndrome with sodium valproate. *Neurology* 1981; **31:** 1162–3.

Myoclonus. Valproate is used alone or in combination with clonazepam for cortical myoclonus (see p.470).

Neuropathic pain. Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p.9), sodium valproate is an alternative antiepileptic that may be used in carbamazepine-intolerant patients. Valproate has also been tried, with some success, in painful *diabetic neuropathy*[1] (p.6), *postherpetic neuralgia*[2] (p.9), and neuropathic *cancer pain*[3] (p.5). However, a placebo-controlled study[4] did not find any benefit with valproate therapy in the treatment of pain in diabetic and nondiabetic polyneuropathy.

1. Kochar DK, *et al.* Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. *QJM* 2004; **97:** 33–8.
2. Kochar DK, *et al.* Divalproex sodium in the management of post-herpetic neuralgia: a randomized double-blind placebo-controlled study. *QJM* 2005; **98:** 29–34.
3. Hardy JR, *et al.* A phase II study to establish the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain. *J Pain Symptom Manage* 2001; **21:** 204–9.
4. Otto M, *et al.* Valproic acid has no effect on pain in polyneuropathy: a randomized, controlled trial. *Neurology* 2004; **62:** 285–8.

Psychiatric disorders. Valproate has psychotropic properties and has been used in the management of bipolar disorder (see above) and in some countries as a mood stabiliser for augmentation of antidepressant therapy in the treatment of resistant depression (p.373). Valproate has also been tried in various disorders for the control of symptoms such as agitation, aggression, and rage[1,2] (see Disturbed Behaviour, p.954). However, a systematic review of the use of valproate for agitation in dementia found no convincing evidence of efficacy at low doses, and adverse effects may be unacceptable at higher doses.[3] Valproate has also been reported[4,5] to be efficacious as adjunctive therapy to antipsychotics, but again, systematic review[6] has thrown doubt upon its effectiveness. It has also been tried in anxiety disorders such as panic disorder[7-9] (p.952), and post-traumatic stress disorder[10,11] (p.953).

1. Geracioti TD. Valproic acid treatment of episodic explosiveness related to brain injury. *J Clin Psychiatry* 1994; **55:** 416–17.
2. Narayan M, *et al.* Treatment of dementia with behavioral disturbances using divalproex or a combination of divalproex and a neuroleptic. *J Clin Psychiatry* 1997; **58:** 351–4.
3. Lonergan ET, Luxenberg J. Valproate preparations for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 09/06/08).
4. Wassef AA, *et al.* Randomized, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *J Clin Psychopharmacol* 2000; **20:** 357–61.
5. Grove VE, *et al.* Improvement of Huntington's disease with olanzapine and valproate. *N Engl J Med* 2000; **343:** 973–4.
6. Basan A, *et al.* Valproate as an adjunct to antipsychotics for schizophrenia: a systematic review of randomized trials. *Schizophr Res* 2004; **70:** 33–7.
7. Primeau F, *et al.* Valproic acid and panic disorder. *Can J Psychiatry* 1990; **35:** 248–50.
8. Keck PE, *et al.* Valproate treatment of panic disorder and lactate-induced panic attacks. *Biol Psychiatry* 1993; **33:** 542–6.
9. Woodman CL, Noyes R. Panic disorder: treatment with valproate. *J Clin Psychiatry* 1994; **55:** 134–6.
10. Fesler FA. Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry* 1991; **52:** 361–4.
11. Petty F, *et al.* Valproate therapy for chronic, combat-induced posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; **22:** 100–101.

Status epilepticus. Valproate has been used in *absence* status epilepticus once the initial attack has been brought under control with intravenous benzodiazepines[1] and has been considered to be the drug of choice to prevent its recurrence.[2] Its place in the management of *convulsive* status epilepticus (p.469) is less clear, but it has been tried, mainly as a second- or third-line drug in benzodiazepine-refractory patients,[3-12] and some centres have included it in management protocols.[5]

1. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
2. Berkovic SF, *et al.* Valproate prevents the recurrence of absence status. *Neurology* 1989; **39:** 1294–7.
3. Giroud M, *et al.* Use of injectable valproic acid in status epilepticus: a pilot study. *Drug Invest* 1993; **5:** 154–9.
4. Hovinga CA, *et al.* Use of intravenous valproate in three pediatric patients with nonconvulsive or convulsive status epilepticus. *Ann Pharmacother* 1999; **33:** 579–84.
5. Campistol J, *et al.* Estado de mal convulsivo en el niño: experiencia con valproato endovenoso, actualización del protocolo de tratamiento. *Rev Neurol* 1999; **29:** 359–65.
6. Peters CNA, Pohlmann-Eden B. Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus—experience in 102 adult patients. *Seizure* 2005; **14:** 164–9.
7. Limdi NA, *et al.* Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005; **64:** 353–5.
8. Limdi NA, *et al.* Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005; **64:** 353–5.
9. Misra UK, *et al.* Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology* 2006; **67:** 340–2.
10. Olsen KB, *et al.* Valproate is an effective, well-tolerated drug for treatment of status epilepticus/serial attacks in adults. *Acta Neurol Scand* 2007; **187** (Suppl): 51–4.
11. Agarwal P, *et al.* Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure* 2007; **16:** 527–32.
12. Mehta V, *et al.* Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. *J Child Neurol* 2007; **22:** 1191–7.

Preparations

BP 2008: Gastro-resistant Sodium Valproate Tablets; Sodium Valproate Oral Solution; Sodium Valproate Tablets;
USP 31: Divalproex Sodium Delayed-Release Tablets; Valproate Sodium Injection; Valproic Acid Capsules; Valproic Acid Syrup.

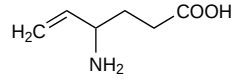
Proprietary Preparations (details are given in Part 3)
Arg.: Depakene; Exibral; Logical; Tekaval†; Valcote; Valnar; ***Austral.:*** Epilim; Valpro; ***Austria:*** Convulex; Depakine; Depakine Chrono; Depakine Chronosphere; Epival†; ***Belg.:*** Convulex; Depakine; ***Braz.:*** Depakene; Depakote; Epilenil; Torval; Valpakine; Valprene; ***Canad.:*** Depakene; Epiject; Epival; ***Chile:*** Atemperator; Depakene; DI VP; Leptilan†; Neuractin; Valcote; ***Cz.:*** Absenor; Convulex; Convulsofin†; Depakine; Depakine Chrono; Everiden; Orfiril; ***Denm.:*** Delepsine; Deprakine; Orfiril; ***Fin.:*** Absenor; Deprakine; Deprakine Depot; Orfiril; ***Fr.:*** Depakine; Depakine Chrono; Depakote; Depamide; Micropakine; ***Ger.:*** Convulex; Convulsofin; Ergenyl; Ergenyl Chrono; Espa-Valept†; Leptilan; Orfiril; Valpro; Valpro Beta; Valprodura; Valproflux†; Valprolept†; ValproNa†; ***Gr.:*** Depakine; Depakine Chrono; ***Hong Kong:*** Epilim; Valpro; ***Hung.:*** Convulex; Depakine; Depakine Chrono; Everiden†; Orfiril; ***India:*** Diproex; Epilex; Valcontin; Valparin; Valrate CR; Valtec; ***Indon.:*** Depakene; Depakote; ***Irl.:*** Epilim; Epilim Chrono; ***Israel:*** Depalept; Depalept Chrono; Orfiril; Valporal; ***Ital.:*** Depakin; Depakin Chrono; Depamag; Depamide; ***Jpn:*** Depakene; ***Malaysia:*** Epilim; Orfiril; ***Mex.:*** Atemperator; Criam; Depakene; Edorame; Epival; Leptilan; Pimiken; Provetal†; Trankitec; Valprosid†; ***Neth.:*** Convulex†; Depakine; Depakine Chrono; Orfiril; Propymal; ***Norw.:*** Deprakine; Orfiril; ***NZ:*** Epilim; ***Philipp.:*** Depakene; Depakote; Epival; ***Pol.:*** Convulex; Depakine; Depakine Chrono; Depakine Chronosphere; Depamide; Dipromal; Orfiril; ***Port.:*** Depakine; Depakine Chrono; Depakine Chronosphere; Diplexil; Diplexil-R; Valprolim; ***Rus.:*** Apilepsin (Апилепсин); Convulex (Конвулекс); Convulsofin (Конвульсофин); Depakine (Депакин); Depakine Chrono (Депакин Хроно); Encorate (Энкорат); Encorate Chrono (Энкорат Хроно); Valparin XR (Вальпарин ХР); ***S.Afr.:*** Convulex; Epilim; ***Singapore:*** Convulex; Epilim; Orfiril†; Valparin; ***Spain:*** Depakine; Depakine Crono; Depamide; Milzone; ***Swed.:*** Absenor; Ergenyl; Orfiril; ***Switz.:*** Convulex; Depakine; Depakine Chrono; Orfiril; ***Thai.:*** Depakine; Desorate; Encorate; Valparin; ***Turk.:*** Convulex; Depakin; ***UAE:*** Valopin; ***UK:*** Convulex; Depakote; Epilim; Epilim Chrono; Episenta; Orlept; ***USA:*** Depacon; Depakene; Depakote; Mendatrex; ***Venez.:*** Depakine; Valcote; Valpron.

Vigabatrin *(BAN, USAN, rINN)*

4-Amino-5-hexenoic Acid; MDL-71754; RMI-71754; Vigabatriini; Vigabatrina; Vigabatrine; Vigabatrinum; γ-Vinyl Aminobutyric Acid; γ-Vinyl-GABA. 4-Aminohex-5-enoic acid.

Вигабатрин

$C_6H_{11}NO_2$ = 129.2.
CAS — 60643-86-9.
ATC — N03AG04.
ATC Vet — QN03AG04.



Pharmacopoeias. In *Br.*
BP 2008 (Vigabatrin). A white to almost white powder. Very soluble in water.

Adverse Effects, Treatment, and Precautions

About half of all patients experience adverse effects with vigabatrin. The most common are drowsiness and fatigue, although in children excitation and agitation occur more frequently. The incidence of these effects is generally higher at the start of therapy and decreases over time. Other CNS-related adverse effects include dizziness, headache, ataxia, paraesthesia, tremor, impaired concentration, confusion, and memory disturbances. Other reported adverse effects include weight gain, gastrointestinal disturbances, oedema, alopecia, angioedema, urticaria, and skin rash. Haemoglobin and liver enzyme values may be decreased. Rarely marked sedation, stupor and confusion, together with other symptoms suggestive of encephalopathy, have occurred.

About one-third of all patients receiving vigabatrin have developed irreversible visual field defects, ranging from mild to severe and usually occurring after months or years of therapy. Blurred vision, diplopia, or nystagmus are somewhat less common. Retinal disorders such as peripheral retinal atrophy, or very rarely optic neuritis or atrophy have also been reported (see also below). Visual field function should be assessed before beginning treatment and during routine follow-up (ideally at 6-month intervals), and patients should be warned to report any new visual symptoms that develop during therapy. Vigabatrin should not be used in patients with pre-existing visual field defects.

Psychiatric reactions such as agitation, aggression, irritability, nervousness, depression, and paranoid reactions have occurred in patients with or without a psychiatric history; psychosis, hypomania, or mania have been reported rarely. Patients receiving vigabatrin should be observed carefully for any signs of adverse effects on neurological function. Caution is warranted in patients with a history of psychosis, depression, or behavioural problems.

Vigabatrin may exacerbate myoclonic or absence seizures.

Vigabatrin should be given with caution to the elderly and patients with renal impairment.

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

Breast feeding. Licensed product information states that breast feeding is not recommended in women receiving vigabatrin. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.
Particular care should be taken in view of the possible effects of vigabatrin on visual acuity.

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

Effects on the eyes. A report of 3 patients who developed bilateral severely constricted visual fields 2 to 3 years after vigabatrin was added to their antiepileptic regimens[1] prompted publication of similar anecdotal reports.[2-5] Peripheral retinal atrophy rather than optic nerve damage appeared to be the cause. Symptoms showed no improvement on stopping the drug, although there was no further deterioration. At that time (1997) the manufacturers replied[6] stating that it was a rare occurrence (less than 0.1%) and was being monitored in further clinical studies. The UK CSM subsequently stated[7] (in March 1998) that it had received 41 reports of visual field defects since December 1989, which persisted in most cases despite stopping treatment. The evidence suggested that the onset of symptoms varied from 1 month to several years after starting vigabatrin. In most cases, visual field defects have persisted despite stopping vigabatrin.[8,9] Interim results of a Prescription Event Monitoring Study[10] in the UK stated that vigabatrin was considered to be probably or possibly associated with objective evidence of a visual field defect in 0.2% of patients. However, subsequent evidence appears to have confirmed that the incidence of visual field defects is much higher;[11-14] revised product literature issued in late 1999 indicated that visual field defects occurred in about one-third of all patients receiving vigabatrin. Male patients appear to be at an increased risk of developing defects.[15,16] Whether cumulative dose may be considered a risk factor remains unclear.[16,17]

The CSM considered[14] that vigabatrin should only be prescribed by a specialist, and only where all other combination therapies have failed. Ophthalmological consultation and visual field as-

sessment should be undertaken before starting vigabatrin and visual field screening repeated at 6-monthly intervals during treatment. Conventional perimetry is unsuitable in patients under 9 years of age, in whom alternative methods should be employed. Opinion amongst some paediatricians[18] was that the risk of developing visual field defects had to be weighed against the potential benefit of seizure control. In very young patients, in whom monitoring of vision was impossible, the benefits of vigabatrin in the treatment of infantile spasms were felt by some to outweigh this risk.[19]

Vigabatrin should not be used in patients with pre-existing visual field defects.[14,18]

1. Eke T, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 180–1.
2. Wilson EA, Brodie MJ. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1693.
3. Wong ICK, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1693–4.
4. Blackwell N, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1694.
5. Harding GFA. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1694.
6. Backstrom JT, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1694–5.
7. Committee of Safety of Medicines/Medicines Control Agency. Vigabatrin (Sabril) and visual field defects. *Current Problems* 1998; **24:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023232&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
8. Hardus P, *et al.* Long term changes in the visual fields of patients with temporal lobe epilepsy using vigabatrin. *Br J Ophthalmol* 2000; **84:** 788–90.
9. Johnson MA, *et al.* Visual function loss from vigabatrin: effect of stopping the drug. *Neurology* 2000; **55:** 40–5.
10. Wilton LV, *et al.* Interim report on the incidence of visual field defects in patients on long term vigabatrin therapy. *Pharmacoepidemiol Drug Safety* 1999; **8** (suppl): S9–S14.
11. Wilton LV, *et al.* Visual field defect associated with vigabatrin: observational cohort study. *BMJ* 1999; **319:** 1165–6.
12. Kälviäinen R, *et al.* Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual defects. *Neurology* 1999; **53:** 922–6.
13. Lawden MC, *et al.* Visual field defects associated with vigabatrin therapy. *J Neurol Neurosurg Psychiatry* 1999; **67:** 716–22.
14. Committee on Safety of Medicines/Medicines Control Agency. Vigabatrin (Sabril): visual field defects. *Current Problems* 1999; **25:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
15. Kälviäinen R, Nousiainen I. Visual field defects with vigabatrin: epidemiology and therapeutic implications. *CNS Drugs* 2001; **15:** 217–30.
16. Wild JM, *et al.* Vigabatrin and epilepsy: lessons learned. *Epilepsia* 2007; **48:** 1318–27.
17. Kinirons P, *et al.* Vigabatrin retinopathy in an Irish cohort: lack of correlation with dose. *Epilepsia* 2006; **47:** 311–17.
18. Appleton RE. Guideline may help in prescribing vigabatrin. *BMJ* 1998; **317:** 1322.
19. Harding GFA. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1998; **316:** 232–3.

Effects on the liver. Vigabatrin has demonstrated *in-vivo* and *in-vitro* inhibition of plasma-alanine transaminase activity, which may mask signs of early underlying hepatic disease if only transaminase levels are evaluated.[1]

1. Richens A, *et al.* Evidence for both in vivo and in vitro interaction between vigabatrin and alanine transaminase. *Br J Clin Pharmacol* 1997; **43:** 163–8.

Effects on mental function. *Behavioural disturbances* ranging from irritability and confusion to psychotic reactions have been reported in patients receiving vigabatrin.[1-7] An analysis[8] of adverse effect reports from double-blind controlled studies found that the incidence of psychotic reactions was about 2.5% in vigabatrin-treated patients; however, the most common psychiatric reaction was depression, which occurred in 8 to 12% of patients. Symptoms of psychiatric disturbance were often relatively mild. Psychiatric reactions are generally reversible when doses are reduced or gradually stopped. In 2 patients[9,10] psychosis developed after sudden withdrawal of vigabatrin; mental state improved when the drug was reinstated. It is not clear whether patients with a history of previous psychiatric disturbances are at greater risk when given vigabatrin.[8,11] Also, using low doses of vigabatrin to start therapy did not reduce the incidence of disturbances.[11]

The problems of antiepileptic therapy adversely affecting *cognition* and *mood* (including the risk of suicidal ideation) are discussed on p.468.

1. Sander JWAS, Hart YM. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 57.
2. Dam M. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 605.
3. Betts T, Thomas L. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 605–6.
4. Johnston SJ. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 606.
5. Robinson MK, *et al.* Vigabatrin and behaviour disturbances. *Lancet* 1990; **336:** 504.
6. Martínez AC, *et al.* Vigabatrin-associated reversible acute psychosis in a child. *Ann Pharmacother* 1995; **29:** 1115–17.
7. Naumann M, *et al.* Bipolar affective psychosis after vigabatrin. *Lancet* 1994; **343:** 606–7.
8. Levinson DF, Devinsky O. Psychiatric adverse events during vigabatrin therapy. *Neurology* 1999; **53:** 1503–11.
9. Ring HA, Reynolds EH. Vigabatrin and behaviour disturbance. *Lancet* 1990; **335:** 970.
10. Brodie MJ, McKee PJW. Vigabatrin and psychosis. *Lancet* 1990; **335:** 1279.
11. Wong ICK. Retrospective study of vigabatrin and psychiatric behavioural disturbances. *Epilepsy Res* 1995; **21:** 227–30.

Effects on the nervous system. Two patients developed disturbances of motor behaviour associated with the addition of vigabatrin to therapy for intractable seizures.[1]

Acute encephalopathy was reported[2] in two patients after starting vigabatrin in addition to carbamazepine; symptoms of stupor, dysphoria, and irritability were present in both and their EEG background activity was slowed. Clinical symptoms could not be related to intoxication with carbamazepine or its epoxide but it was not known whether an interaction between carbamazepine and vigabatrin had caused the acute encephalopathy. Acute encephalopathy was also reported[3] when vigabatrin was given to a 6-month-old girl who was also receiving phenobarbital. Symptoms resolved when vigabatrin was stopped. In another report[4] vigabatrin was associated with the development of encephalopathy in 3 patients already receiving a variety of antiepileptic drugs other than carbamazepine; withdrawal of vigabatrin led to full recovery. The authors suggested that acute encephalopathy after vigabatrin may be related to a pre-existing cerebral abnormality. Other predisposing factors suggested by licensed product information include higher than recommended initial doses, faster dose increases at greater increments than those recommended, and renal failure.

1. Jongsma MJ, *et al.* Reversible motor disturbances induced by vigabatrin. *Lancet* 1991; **338:** 893.
2. Sälke-Kellermann A, Baier H. Acute encephalopathy with vigabatrin. *Lancet* 1993; **342:** 185.
3. Haas-Lude K, *et al.* Acute encephalopathy associated with vigabatrin in a six-month-old girl. *Epilepsia* 2000; **41:** 628–30.
4. Sharief MK, *et al.* Acute encephalopathy with vigabatrin. *Lancet* 1993; **342:** 619.

Interference with diagnostic tests. Vigabatrin can cause changes in the urinary excretion of amino acids which could be potentially misleading in patients undergoing investigation for metabolic disorders.[1,2]

1. Bonham JR, *et al.* Pyroglutamicaciduria from vigabatrin. *Lancet* 1989; **i:** 1452–3.
2. Shih VE, Tenanbaum A. Aminoaciduria due to vinyl-gaba administration. *N Engl J Med* 1990; **323:** 1353.

Overdosage. For a review of the features and management of poisoning with some antiepileptics such as vigabatrin, see under Phenytoin, p.497.

Porphyria. For comment on the use of vigabatrin in porphyria, see p.471.

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

Little is known of the effects of newer antiepileptics such as vigabatrin on the fetus, although congenital anomalies have been reported in the offspring of some mothers using vigabatrin during pregnancy.

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.

Antiepileptics. For the effect of vigabatrin on plasma concentrations of other antiepileptics, see *Carbamazepine*, p.474; *Phenobarbital*, p.493; *Phenytoin*, p.498; and *Primidone*, p.503.

Pharmacokinetics

Vigabatrin is well absorbed after oral doses of the racemate; the inactive *R*(−)-enantiomer is reported to be present at much higher plasma concentrations than the active *S*(+)-enantiomer, perhaps indicating a difference in bioavailability. About 60 to 80% of an oral dose is excreted in urine as unchanged drug. The elimination half-life is reported to be 5 to 8 hours. Vigabatrin is not significantly bound to plasma proteins.

There does not appear to be any correlation between plasma concentrations of vigabatrin and its efficacy or toxicity. Children exhibit a lower area under the concentration-time curve than adults and may need higher doses to achieve therapeutic plasma concentrations.

Vigabatrin crosses the placenta and is distributed into breast milk.

◊ References.

1. Rey E, *et al.* Vigabatrin: clinical pharmacokinetics. *Clin Pharmacokinet* 1992; **23:** 267–78.
2. Hoke JF, *et al.* Pharmacokinetics of vigabatrin following single and multiple oral doses in normal volunteers. *J Clin Pharmacol* 1993; **33:** 458–62.
3. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
4. Vauzelle-Kervroëdan F, *et al.* Pharmacokinetics of the individual enantiomers of vigabatrin in neonates with uncontrolled seizures. *Br J Clin Pharmacol* 1996; **42:** 779–81.
5. Jacqz-Aigrain E, *et al.* Pharmacokinetics of the S(+) and R(−) enantiomers of vigabatrin during chronic dosing in a patient with renal failure. *Br J Clin Pharmacol* 1997; **44:** 183–5.
6. Armijo JA, *et al.* Vigabatrin serum concentration to dosage ratio: influence of age and associated antiepileptic drugs. *Ther Drug Monit* 1997; **19:** 491–8.
7. Tran A, *et al.* Vigabatrin: placental transfer in vivo and excretion into breast milk of the enantiomers. *Br J Clin Pharmacol* 1998; **45:** 409–11.

Uses and Administration

Vigabatrin is an analogue of gamma-aminobutyric acid (GABA) that acts as an irreversible inhibitor of GABA-transaminase, the enzyme responsible for the catabolism of GABA. It is used as an adjunctive antiepileptic in patients with resistant partial epilepsy with or without secondary generalisation, unresponsive to other therapy. It is also used as monotherapy for infantile spasms (as for example in West's syndrome).

The recommended initial oral dose of vigabatrin as adjunctive therapy is 1 g daily, increased, according to response and tolerability, in increments of 500 mg at weekly intervals to a maximum of 3 g daily.

Doses may be divided and given twice daily or taken as a single daily dose. Dosage reductions may be required in the elderly and in patients with renal impairment, particularly those with a creatinine clearance of less than 60 mL/minute.

For details of doses in children, see below.

As with other antiepileptics, withdrawal of vigabatrin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465. Licensed product information recommends that the dose of vigabatrin should be gradually reduced over 2 to 4 weeks.

◊ References.

1. Wheless JW, *et al.* Vigabatrin. *Neurotherapeutics* 2007; **4:** 163–72.

Administration in children. Vigabatrin is used as an adjunctive antiepileptic in children with resistant partial epilepsy with or without secondary generalisation, unresponsive to other therapy. It is also used as monotherapy for infantile spasms (as for example in West's syndrome).

The recommended initial oral dose of vigabatrin as *adjunctive therapy* is 40 mg/kg daily, as a single dose or in 2 divided doses. Maintenance doses are given according to body-weight as follows:

- 10 to 15 kg: 0.5 to 1 g daily
- 15 to 30 kg: 1 to 1.5 g daily
- 30 to 50 kg: 1.5 to 3 g daily
- over 50 kg: 2 to 3 g daily

Alternatively, the *BNFC* suggests giving the following oral doses according to age:

- neonates to 12 years: initially 15 to 20 mg/kg twice daily, increased over 2 to 3 weeks to a usual maintenance dose of 30 to 40 mg/kg twice daily; maximum 150 mg/kg daily
- 12 to 18 years: initially 1 g twice daily, increased over 2 to 3 weeks to a usual maintenance dose of 1 to 1.5 g twice daily

Vigabatrin has been given rectally; in the UK, the *BNFC* has suggested that children over 1 month old may be given the same rectal doses, calculated by age, as those used orally (see above). The commercially available oral powder should be dissolved in a small amount of water before use.

For *monotherapy* in infantile spasms, the recommended initial oral dose of vigabatrin is 50 mg/kg daily, adjusted according to response. Up to 150 mg/kg daily has been used. The *BNFC* suggests starting with 15 to 25 mg/kg twice daily, adjusted according to response over 7 days; the usual maintenance dose is 40 to 50 mg/kg twice daily (maximum of 75 mg/kg twice daily) for neonates and children up to 2 years of age.

Epilepsy. Vigabatrin is used in the treatment of epilepsy (p.465) as adjunctive therapy for refractory seizures. Reviews[1-3] of vigabatrin have considered it to be most effective in the treatment of complex partial seizures with or without secondary generalisation; it may, however, exacerbate myoclonic or absence seizures. Efficacy as adjunctive therapy in refractory partial seizures was shown by 2 multicentre studies[4,5] involving 228 patients (including 46 children) and a study[6] involving 52 patients being assessed for epilepsy surgery. However, in a follow-up study[7] of 120 patients who had participated in an open-label study of vigabatrin as adjunctive therapy for refractory epilepsy 6 to 8 years earlier, it was considered that vigabatrin had had only marginal benefit on the long-term prognosis of severe refractory epilepsy, despite favourable results from the original trial.

Vigabatrin is also of value in infantile spasms (as for example in West's syndrome). In an assessment of vigabatrin as monothera-

py in 192 infants with infantile spasms who were followed up for an average of 7.6 months,[8] there was complete cessation of spasms in 131 patients, a decrease in cluster frequency in 37, and no improvement in 24 (including deterioration in 1 infant). A crossover study comparing vigabatrin with corticotropin in 42 infants found that both drugs produced some benefit;[9] a larger multicentre comparison of treatment with prednisolone and tetracosactide versus vigabatrin found that the former produced better initial control, but that the treatments were equivalent after more prolonged follow-up to 12 to 14 months of age.[10] A review of the literature suggested that vigabatrin was particularly effective in infantile spasms associated with tuberous sclerosis;[11] the authors considered that its efficacy might be less in other forms of infantile spasm.[11] A later guideline[12] also tentatively concluded that vigabatrin was effective in the short-term treatment of infantile spasms including those associated with tuberous sclerosis.

1. French JA. Vigabatrin. *Epilepsia* 1999; **40** (suppl 5): S11–S16.
2. Gidal BE, *et al.* Vigabatrin: a novel therapy for seizure disorders. *Ann Pharmacother* 1999; **33:** 1277–86.
3. Lewis H, Wallace SJ. Vigabatrin. *Dev Med Child Neurol* 2001 **43:** 833–5.
4. Dalla Bernadina B, *et al.* Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. *Epilepsia* 1995; **36:** 687–91.
5. French JA, *et al.* A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. *Neurology* 1996; **46:** 54–61.
6. Malmgren K, *et al.* Cost analysis of epilepsy surgery and of vigabatrin treatment in patients with refractory partial epilepsy. *Epilepsy Res* 1996; **25:** 199–207.
7. Walker MC, *et al.* Long term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome. *BMJ* 1996; **313:** 1184–5.
8. Aicardi J, *et al.* Sabril IS Investigator and Peer Review Groups. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. *Epilepsia* 1996; **37:** 638–42.
9. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. *Epilepsia* 1997; **38:** 1270–4.
10. Lux AL, *et al.* The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *Lancet Neurol* 2005; **4:** 712–17.
11. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis. *J Child Neurol* 1999; **14:** 71–4.
12. Mackay MT, *et al.* Practice parameter: medical treatment of infantile spasms—report of the American Academy of Neurology and the Child Neurology Society. *Neurology* 2004; **62:** 1668–81.

Metabolic disorders. Vigabatrin, an irreversible inhibitor of GABA-transaminase, has been tried in GABA metabolic disorders, with or without concurrent epilepsy,[1-5] with ambivalent results. Data from 23 case reports of patients with succinic semialdehyde dehydrogenase deficiency indicated that vigabatrin was clinically beneficial in only about one-third of patients.[4]

1. Jaeken J, *et al.* Vigabatrin in GABA metabolism disorders. *Lancet* 1989; **i**: 1074.
2. Gibson KM, *et al.* Vigabatrin therapy in patient with succinic semialdehyde dehydrogenase deficiency. *Lancet* 1989; **ii:** 1105–6.
3. Stephenson JBP. Vigabatrin for startle-disease with altered cerebrospinal-fluid free gamma-aminobutyric acid. *Lancet* 1992; **340:** 430–1.
4. Gibson KM, *et al.* The clinical phenotype of succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria): case reports of 23 new patients. *Pediatrics* 1997; **99:** 567–74.
5. Leuzzi V, *et al.* Vigabatrin improves paroxysmal dystonia in succinic semialdehyde dehydrogenase deficiency. *Neurology* 2007; **68:** 1320–1.

Stiff-man syndrome. There have been anecdotal reports[1-3] of improvement of stiff-man syndrome (see under Muscle Spasm, p.993) with vigabatrin in patients unable to tolerate benzodiazepine therapy.

1. Vermeij FH, *et al.* Improvement of stiff-man syndrome with vigabatrin. *Lancet* 1996; **348:** 612.
2. Prevett MC, *et al.* Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1997; **48:** 1133–4.
3. Sharoqi IA. Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1998; **50:** 833–4.

Preparations

BP 2008: Vigabatrin Oral Powder; Vigabatrin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Sabril; ***Austral.:*** Sabril; ***Austria:*** Sabril; ***Belg.:*** Sabril; ***Braz.:*** Sabril; ***Canad.:*** Sabril; ***Chile:*** Sabril; ***Cz.:*** Sabril; ***Denm.:*** Sabrilex; ***Fin.:*** Sabrilex; ***Fr.:*** Sabril; ***Ger.:*** Sabril; ***Gr.:*** Sabril; ***Hong Kong:*** Sabril; ***Hung.:*** Sabril; ***Irl.:*** Sabril; ***Israel:*** Sabrilan; ***Ital.:*** Sabril; ***Mex.:*** Sabril; ***Neth.:*** Sabril; Sabrilex; ***Norw.:*** Sabrilex; ***NZ:*** Sabril; ***Pol.:*** Sabril; ***Port.:*** Sabril; ***S.Afr.:*** Sabril; ***Singapore:*** Sabril; ***Spain:*** Sabrilex; ***Swed.:*** Sabrilex; ***Switz.:*** Sabril; ***Turk.:*** Sabril; ***UK:*** Sabril.

Zonisamide *(BAN, USAN, rINN)*

AD-810; CI-912; PD-110843; Zonisamida; Zonisamidum. 1-(1,2-Benzoxazol-3-yl)methanesulphonamide.

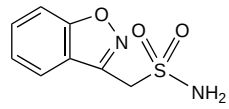
Зонизамид

$C_8H_8N_2O_3S$ = 212.2.

CAS — 68291-97-4.

ATC — N03AX15.

ATC Vet — QN03AX15.



Adverse Effects

The most common adverse effects with zonisamide have included anorexia, gastrointestinal disturbances such as abdominal pain, diarrhoea, and nausea, somnolence, dizziness, headache, ataxia, depression, and agitation or irritability. Severe, sometimes fatal, skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely. There have been isolated reports of aplastic anaemia, agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, and leucocytosis.

Other adverse effects have included renal calculi (see below), renal impairment, pancreatitis, rhabdomyolysis, abnormal liver function tests, psychosis, psychomotor slowing, reduced concentration, speech or language difficulties, paraesthesia, nystagmus, diplopia, weight loss, and fatigue. Reduced sweating with hyperthermia has occurred in children (see below).

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

Hyperthermia. Decreased sweating and hyperthermia have been reported in patients given zonisamide. By the end of December 2001 the manufacturers in the USA were aware of 40 such cases; of these, 38 had occurred in the first 11 years of marketing in Japan and 2 in the first year of marketing in the USA. Many cases were reported after exposure to high ambient temperatures and some progressed to heat stroke, but none had led to death.

The manufacturer noted that children appeared to be at an increased risk of developing these adverse reactions and should be monitored closely for such effects especially during warm or hot weather. Caution was also advised when zonisamide was given with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.[1]

1. O'Brien C [Elan Pharmaceuticals]. Important drug warning. Available at: http://www.fda.gov/medwatch/SAFETY/2002/Zonegran_deardoc.pdf (accessed 14/05/04)

Renal calculi. Patients treated with zonisamide in the USA and Europe may have had a higher incidence of renal calculi than those treated in Japan. In one US study,[1] 4 of 113 patients (3.5%) receiving long-term treatment with zonisamide developed renal calculi, but a familial relationship was found for 2. In pooled data[2] from earlier studies, renal calculi had been reported in 13 of 700 patients (1.9%) treated in the USA and Europe compared with 2 of 1008 patients (0.2%) in Japan. Another review,[3] involving information from more than 750 patients, considered the risk of renal calculi in zonisamide-treated patients to be 5 to 9 times greater than that in the general population. However, a later study[4] that evaluated all safety data available at the time (from the US and European clinical trial programme and the manufacturer's postmarketing surveillance database) found the prevalence of symptomatic renal calculi to be low. There has been a report[5] of 3 patients who developed renal calculi associated with zonisamide but were able to continue therapy with hydration and/or citrate supplementation.

1. Patsalos PN, Sander JWAS. Newer antiepileptic drugs: towards an improved risk-benefit ratio. *Drug Safety* 1994; **11:** 37–67.
2. Peters DH, Sorkin EM. Zonisamide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993; **45:** 760–87.
3. Bennett WM. Risk of kidney stones in patients treated with zonisamide. *Neurology* 2002; **58** (suppl 3): A298–A299.
4. Wroe S. Zonisamide and renal calculi in patients with epilepsy: how big an issue? *Curr Med Res Opin* 2007; **23:** 1765–73.
5. Richards KC, *et al.* Continued use of zonisamide following development of renal calculi. *Neurology* 2005; **64:** 763–4.

Precautions

Zonisamide is a sulfonamide derivative and is therefore contra-indicated in patients with a history of hypersensitivity to sulfonamides.

It should be used with care in patients with renal impairment; there is no data on safety in those with hepatic impairment. Zonisamide should be used with caution in patients who have risk factors for nephrolithiasis; adequate hydration is recommended to increase urine output, to try to reduce the risk of developing renal calculi, especially in predisposed patients.

Pancreatic lipase and amylase levels should be monitored in patients who develop pancreatitis and consideration should be given to withdrawing zonisamide. Patients who develop severe muscle pain or weakness, with or without fever, should have their serum creatine phosphokinase and aldolase levels assessed; if these are elevated, zonisamide may need to be withdrawn. A dietary supplement or increased food intake may be appropriate in patients who are losing weight or are underweight with zonisamide; withdrawing zonisamide may be warranted in those with substantial undesirable weight loss. Consideration should be given to withdrawing zonisamide in patients who develop unexplained rash.

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

Breast feeding. Zonisamide is distributed into breast milk;[1] in view of the potential for serious adverse effects in infants from zonisamide, licensed product information recommends that it should only be used in nursing mothers if the benefits outweigh the risks. It is also recommended that breast feeding must not be resumed until 1 month after stopping zonisamide therapy. For comment on antiepileptic therapy and breast feeding, see p.467.

1. Kawada K, *et al.* Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; **24:** 95–7.

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

Pregnancy. Zonisamide crosses the placenta.[1] For comments on the management of epilepsy during pregnancy, see p.468.

1. Kawada K, *et al.* Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; **24:** 95–7.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Use with drugs that induce or inhibit the cytochrome P450 isoenzyme CYP3A4 may alter plasma concentrations of zonisamide. Carbamazepine, phenytoin, or phenobarbital reduce the half-life of zonisamide; reductions have also been noted with valproate but to a lesser degree.

The use of zonisamide with other drugs that cause nephrolithiasis should be avoided because of the increased risk of developing renal calculi (see under Adverse Effects, above). Caution is advised when zonisamide is used with other drugs known to cause heat-related disorders because of the increased risk of developing hyperthermia (see Adverse Effects, above).

◊ References.

1. Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007; **48:** 435–41.

Pharmacokinetics

Zonisamide is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within 2 to 6 hours of oral doses. Bioavailability is essentially complete; the presence of food does not affect the bioavailability of zonisamide but the time to reach peak plasma concentrations is delayed. Steady-state concentrations are achieved within 14 days. It is widely distributed into body tissues. Plasma protein binding is low (40 to 50%) but zonisamide is extensively bound to erythrocytes. The plasma elimination half-life is about 63 hours.

Zonisamide undergoes acetylation to *N*-acetylzonisamide and reduction mediated by the cytochrome P450 isoenzyme CYP3A4 to 2-sulfamoylacetylphenol (SMAP); both metabolites are inactive. Excretion is mainly in the urine; about 15 to 30% appearing as