Tiagabine Hydrochloride

(BANM, USAN, rINNM)

Abbott-70569.1; ABT-569; Hidrocloruro de tiagabina; NNC-05-0328; NO-05-0328; Tiagabine, Chlorhydrate de; Tiagabini Hydrochloridum. (–)-(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-nipecotic acid hydrochloride.

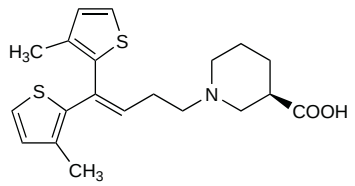
Тиагабина Гидрохлорид

$C_{20}H_{25}NO_2S_2,HCl$ = 412.0.

CAS — 115103-54-3 (tiagabine); 145821-59-6 (tiagabine hydrochloride).

ATC — N03AG06.

ATC Vet — QN03AG06.



(tiagabine)

Pharmacopoeias. In *US.*

USP 31 (Tiagabine Hydrochloride). A white to off-white powder. Sparingly soluble in water; freely soluble in alcohol and methyl alcohol; soluble in isopropyl alcohol; very slightly soluble in chloroform; practically insoluble in *n*-heptane. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Stability. An extemporaneously prepared suspension containing tiagabine hydrochloride 1 mg/mL in a mixture of simple syrup and 1% methylcellulose was found,[1] when stored in plastic amber bottles, to be stable for 6 weeks at 25° or 13 weeks at 4°. When prepared in a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (*Paddock, USA*), the suspension was stable for 10 weeks at 25° or 13 weeks at 4°.

1. Nahata MC, Morosco RS. Stability of tiagabine in two oral liquid vehicles. *Am J Health-Syst Pharm* 2003; **60:** 75–7.

Adverse Effects

The most common adverse effects include dizziness, nervousness, tiredness, somnolence, and tremor. Other reported adverse effects include irritability, confusion, depression, psychosis, difficulties in concentration, diarrhoea, abdominal pain, nausea, ataxia, emotional lability, and nystagmus. Bruising, rashes, speech difficulties, and a flu-like syndrome of chills, fever, myalgia, and headache have also been reported. Visual field defects have been reported rarely and decreased white blood cell counts have been noted at routine screenings.

Incidence of adverse effects. A systematic review[1] considered 5 double-blind studies involving about 1000 patients of whom 675 were receiving tiagabine as adjunctive therapy for refractory partial seizures. Withdrawal due to adverse effects was infrequent and occurred in 15% of patients receiving tiagabine compared with 5% receiving placebo. Adverse effects were usually associated with dose titration, and were generally mild to moderate in severity, and transient. Another review[2] by the same author on data from all clinical studies (52 studies involving nearly 3100 patients) reported that in 21% of patients receiving tiagabine had the drug stopped for adverse effects, mostly during the first 6 months of therapy. Sub-analysis showed that figures for placebo-controlled, adjunctive studies were similar to those of the earlier review.

1. Leppik IE. Tiagabine: the safety landscape. *Epilepsia* 1995; **36** (suppl 6): S10–S13.
2. Leppik IE, *et al.* Safety of tiagabine: summary of 53 trials. *Epilepsy Res* 1999; **33:** 235–46.

Effects on the eyes. Unlike vigabatrin, which is associated with visual field defects (see p.513), studies of visual function in patients taking tiagabine, another GABAergic antiepileptic, have been generally reassuring. However, in a case report[1] a 39-year-old patient was noted to have visual field defects while receiving long-term tiagabine therapy for bipolar disorder. The defects reversed after tiagabine was withdrawn.

1. Kaufman KR, *et al.* Visual fields and tiagabine: a quandary. *Seizure* 2001; **10:** 525–9.

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

Effects on the nervous system. Acute dystonic reactions occurred in 3 patients when tiagabine was added to their existing carbamazepine treatment;[1] the reactions were associated with an increase in the dose of tiagabine to 20 mg or more. In all cases the dystonias disappeared despite continuing tiagabine therapy at the same dose, although in one patient carbamazepine was withdrawn.

There have been case reports of nonconvulsive status epilepticus,[2-4] associated with tiagabine. The authors of one such report[2] noted that, in placebo-controlled studies, the incidence of such an event was no higher in the tiagabine group than in the placebo group. However, a retrospective analysis[5] of inpatients with refractory localised epilepsy found that non convulsive status epilepticus occurred more frequently in patients treated with tiagabine (6.7%) than in those who were not (1.1%).

The FDA has warned of the risk of seizures with tiagabine when used in *non-epileptic patients* for unlicensed indications;[6] it had received over 30 reports of new-onset seizures or status epilepticus in such patients. Predisposing factors may include the use of other drugs known to lower the seizure threshold, and probably the dose. Although some cases were noted after doses as low as 4 mg daily, licensed doses in patients with epilepsy take into account the customary use of other enzyme-inducing antiepileptics which can roughly halve the plasma levels of tiagabine by inducing its metabolism. For reports of status epilepticus occurring in non-epileptic patients after tiagabine overdosage, see below.

1. Wolańczyk T, Grabowska-Grzyb A. Transient dystonias in three patients treated with tiagabine. *Epilepsia* 2001; **42:** 944–6.
2. Fitzek S, *et al.* Drug-induced nonconvulsive status epilepticus with low dose of tiagabine. *Epileptic Disord* 2001; **3:** 147–50.
3. Skardoutsou A, *et al.* Non-convulsive status epilepticus associated with tiagabine therapy in children. *Seizure* 2003; **12:** 599–601.
4. Vinton A, *et al.* Tiagabine-induced generalised non convulsive status epilepticus in patients with lesional focal epilepsy. *J Clin Neurosci* 2005; **12:** 128–33.
5. Koepp MJ, *et al.* Status epilepticus and tiagabine therapy revisited. *Epilepsia* 2005; **46:** 1625–32.
6. Food and Drug Administration. Tiagabine hydrochloride (marketed as Gabitril): seizures in patients without epilepsy (issued 18/02/05). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/TiagabineHCP.pdf (accessed 09/06/08)

Overdosage. A 30-year-old man who took 320 mg of tiagabine in overdose together with 400 mg of phenytoin showed no serious signs of toxicity other than significantly depressed levels of consciousness from which he quickly recovered.[1] Plasma concentrations of tiagabine measured 4 hours after ingestion were 30 times higher than those seen with therapeutic doses; phenytoin concentrations just exceeded the therapeutic range. A 46-year-old woman[2] who ingested about 72 mg of tiagabine exhibited facial grimacing, rigid flexure posturing of the upper extremities, and dilated pupils. She was uncommunicative and unresponsive to commands. Treatment with benzodiazepines was given, and symptoms resolved within 12 hours of admission.

Seizures, including status epilepticus, are a recognised adverse effect of tiagabine (see above); there have been reports of status epilepticus occurring in non-epileptic patients after overdosage, including non convulsive status epilepticus[3] in a 14-year-old girl who took about 180 mg of tiagabine, and myoclonic status epilepticus[4] in an 18-year-old man who took 120 mg of tiagabine with 400 mg of lamotrigine.

A retrospective review[5] of 57 overdoses with tiagabine reported to several poison centres in the USA found that the most common adverse effects were lethargy (in 56%), seizures (37%, including status epilepticus in 5%), agitation (32%), confusion (30%), and coma (28%). Other adverse effects included tachycardia, respiratory depression, tremor, and hallucinations; no deaths were reported. The mean onset and duration of symptoms were 1.3 and 9.1 hours, respectively. The lowest dose associated with seizures was 96 mg.

1. Leach JP, *et al.* Deliberate overdose with the novel anticonvulsant tiagabine. *Seizure* 1995; **4:** 155–7.
2. Cantrell FL, *et al.* Intentional overdose with tiagabine: an unusual clinical presentation. *J Emerg Med* 2004; **27:** 271–2.
3. Jette N, *et al.* Tiagabine-induced nonconvulsive status epilepticus in an adolescent without epilepsy. *Neurology* 2006; **67:** 1514–15.
4. Vollmar C, Noachtar S. Tiagabine-induced myoclonic status epilepticus in a nonepileptic patient. *Neurology* 2007; **68:** 310.
5. Spiller HA, *et al.* Retrospective evaluation of tiagabine overdose. *Clin Toxicol* 2005; **43:** 855–9.

Precautions

Hepatic metabolism of tiagabine is reduced in patients with hepatic impairment, and dosage should therefore be reduced and/or the intervals between doses increased. It should not be used in patients with severely impaired hepatic function.

Use of tiagabine in non-epileptic patients may be associated with an increased risk of seizures— see Effects on the Nervous System, above.

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

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

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

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 hepatic metabolism of tiagabine is accelerated by antiepileptics that induce enzymes of the cytochrome P450 system such as carbamazepine, phenobarbital, phenytoin, or primidone. Plasma concentrations of tiagabine may be reduced up to threefold by use with these drugs.

Pharmacokinetics

Tiagabine is readily absorbed after oral doses, with a bioavailability of 89%. Food reduces the rate but not the extent of absorption. The absorption and elimination pharmacokinetics of tiagabine are linear within the therapeutic dosage range.

Tiagabine is widely distributed throughout the body and plasma protein binding is 96%.

Tiagabine is extensively metabolised in the liver and excreted as metabolites in the faeces or, to a lesser extent, in the urine; less than 2% of a dose is eliminated as unchanged drug. The plasma-elimination half-life is 7 to 9 hours, although this may be reduced to 2 to 3 hours by liver enzyme-inducing drugs (see also Interactions, above).

◊ References.

1. Gustavson LE, Mengel HB. Pharmacokinetics of tiagabine, a γ-aminobutyric acid-uptake inhibitor, in healthy subjects after single and multiples doses. *Epilepsia* 1995; **36:** 605–11.
2. So EL, *et al.* Pharmacokinetics of tiagabine as add-on therapy in patients taking enzyme-inducing antiepilepsy drugs. *Epilepsy Res* 1995; **22:** 221–6.
3. Snel S, *et al.* The pharmacokinetics of tiagabine in healthy elderly volunteers and elderly patients with epilepsy. *J Clin Pharmacol* 1997; **37:** 1015–20.
4. Cato A, *et al.* Effect of renal impairment on the pharmacokinetics and tolerability of tiagabine. *Epilepsia* 1998; **39:** 43–7.
5. Samara EE, *et al.* Population analysis of the pharmacokinetics of tiagabine in patients with epilepsy. *Epilepsia* 1998; **39:** 868–73.

Uses and Administration

Tiagabine is a nipecotic acid derivative used in the treatment of epilepsy (p.465) as adjunctive therapy for refractory partial seizures with or without secondary generalisation. It inhibits the uptake of GABA into neuronal and glial cells, and therefore increases the availability of GABA at receptor sites.

UK licensing information states that tiagabine hydrochloride is given as the monohydrate, but doses are described in terms of tiagabine; dose forms providing the equivalent of 5, 10, and 15 mg of tiagabine are available. In the USA, however, the licensed product is stated to contain anhydrous tiagabine hydrochloride, and doses are described in terms of this substance; dose forms providing 2, 4, 12, and 16 mg are available. As a result, the doses in the UK and US literature may not be directly comparable.

In the UK, the initial oral daily dose as adjunctive therapy in adults and children over 12 years of age is the equivalent of tiagabine 5 to 10 mg as a single dose or in 2 divided doses, increased weekly as necessary by increments of 5 to 10 mg. The usual maintenance dose is 30 to 45 mg daily, in 2 or 3 divided doses, in patients receiving enzyme-inducing antiepileptics; in patients *not* taking enzyme-inducing drugs an initial maintenance dosage of 15 to 30 mg daily is suggested. Lower initial doses of the hydrochloride are recommended in the USA. Doses should be taken with food to avoid rapid rises in plasma concentrations, thereby reducing the incidence of adverse effects. Reduced doses should be given in hepatic impairment—see below.

As with other antiepileptics, withdrawal of tiagabine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends gradual

withdrawal over a period of 2 to 3 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Administration in hepatic impairment. The initial daily maintenance dosage of tiagabine in patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9) should be reduced to 5 to 10 mg given as a single dose or in 2 divided doses. Tiagabine should not be given to patients with severe hepatic impairment.

Epilepsy. Tiagabine is one of a number of drugs that may be used as adjunctive therapy in patients with partial seizures (with or without secondary generalisation) refractory to standard treatment (p.465). It appears to be reasonably well tolerated. For the suggestion that it might be tried in refractory status epilepticus, see p.469.

References.

1. Leach JP, Brodie MJ. Tiagabine. *Lancet* 1998; **351:** 203–7.
2. Adkins JC, Noble S. Tiagabine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. *Drugs* 1998; **55:** 437–60.
3. Luer MS, Rhoney DH. Tiagabine: a novel antiepileptic drug. *Ann Pharmacother* 1998; **32:** 1173–80.
4. Loiseau P. Review of controlled trials of gabitril (tiagabine): a clinician's viewpoint. *Epilepsia* 1999; **40** (suppl 9): S14–S19.
5. Anonymous. Tiagabine: add-on treatment for partial seizures. *Drug Ther Bull* 2000; **38:** 47–8.
6. Dodrill CB, *et al.* Tiagabine versus phenytoin and carbamazepine as add-on therapies: effects on abilities, adjustment, and mood. *Epilepsy Res* 2000; **42:** 123–32.
7. Crawford P, *et al.* Tiagabine: efficacy and safety in adjunctive treatment of partial seizures. *Epilepsia* 2001; **42:** 531–8.
8. Biraben A, *et al.* Comparison of twice- and three times daily tiagabine for the adjunctive treatment of partial seizures in refractory patients with epilepsy: an open label, randomised, parallel-group study. *Epileptic Disord* 2001; **3:** 91–100.
9. Pereira J, *et al.* Tiagabine add-on for drug-resistant partial epilepsy. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 09/06/08).
10. Arroyo S, *et al.* A randomised open-label study of tiagabine given two or three times daily in refractory epilepsy. *Seizure* 2005; **14:** 81–4.

Pain. Antiepileptics are among the drugs used to manage pain (see Choice of Analgesic, p.2); tiagabine has been tried in chronic pain[1] and was found to be effective.

1. Todorov AA, *et al.* Tiagabine and gabapentin for the management of chronic pain. *Clin J Pain* 2005; **21:** 358–61.

Psychiatric disorders. Tiagabine has been tried for the treatment of *generalised anxiety disorder*[1,2] (p.952) and *major depressive disorder* with anxiety[3] (p.373), with variable results. It has also been tried in *post-traumatic stress disorder* (p.953) with some success in a case series[4] and a small open-label study[5] although a later multicentre placebo-controlled study[6] found no significant difference between tiagabine and placebo; further studies are considered warranted. A preliminary study[7] suggested that tiagabine may be effective and generally well tolerated as augmentation therapy in patients with anxiety disorders.

References.

1. Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry* 2003; **64:** 1245–9.
2. Pollack MH, *et al.* The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: results of a placebo-controlled study. *J Clin Psychiatry* 2005; **66:** 1401–8.
3. Carpenter LL, *et al.* Open-label tiagabine monotherapy for major depressive disorder with anxiety. *J Clin Psychiatry* 2006; **67:** 66–71.
4. Taylor FB. Tiagabine for posttraumatic stress disorder: a case series of 7 women. *J Clin Psychiatry* 2003; **64:** 1421–5.
5. Connor KM, *et al.* Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. *Psychopharmacology (Berl)* 2006; **184:** 21–5.
6. Davidson JRT, *et al.* The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. *J Clin Psychopharmacol* 2007; **27:** 85–8.
7. Schwartz TL, *et al.* An open-label study of tiagabine as augmentation therapy for anxiety. *Ann Clin Psychiatry* 2005; **17:** 167–72.

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

1. Murinson BB, Rizzo M. Improvement of stiff-person syndrome with tiagabine. *Neurology* 2001; **57:** 366.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Gabitril; ***Austria:*** Gabitril; ***Belg.:*** Gabitril; ***Cz.:*** Gabitril; ***Denm.:*** Gabitril; ***Fin.:*** Gabitril†; ***Fr.:*** Gabitril; ***Ger.:*** Gabitril; ***Gr.:*** Gabitril; ***Hung.:*** Gabitril; ***Irl.:*** Gabitril; ***Ital.:*** Gabitril; ***Mex.:*** Gabatril†; ***Pol.:*** Gabitril; ***Port.:*** Gabitril; ***Spain:*** Gabitril; ***Switz.:*** Gabitril; ***UK:*** Gabitril; ***USA:*** Gabitril.

Topiramate *(BAN, USAN, rINN)*

KW-6485; McN-4853; RWJ-17021; Topiramaatti; Topiramat; Topiramato; Topiramatum. 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulphamate.

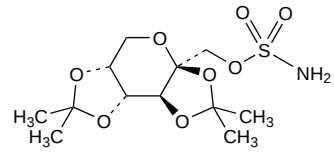
Топирамат

$C_{12}H_{21}NO_8S$ = 339.4.

CAS — 97240-79-4.

ATC — N03AX11.

ATC Vet — QN03AX11.



Pharmacopoeias. In *US.*

USP 31 (Topiramate). A white to off-white powder. Freely soluble in dichloromethane. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

Adverse effects associated with topiramate therapy include ataxia, impaired concentration, confusion, dizziness, fatigue, paraesthesia or hypoaesthesia, drowsiness, and difficulties with memory or cognition. Agitation, anxiety, nervousness, emotional lability, and mood disorders may also occur. Other reported adverse effects include abdominal pain, anorexia, asthenia, diplopia, leucopenia, nausea, nystagmus, insomnia, psychomotor retardation, impaired speech, altered taste, visual disturbances, and weight loss. The risk of developing renal calculi is increased, especially in predisposed patients. Reduced sweating with hyperthermia has occurred particularly in children. Rare cases of acute myopia with secondary angle-closure glaucoma have been reported.

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

Effects on electrolytes. Metabolic acidosis has been associated with topiramate treatment. Data from clinical trials estimate that the incidence of persistently decreased serum bicarbonate concentrations ranges from 23 to 67% with topiramate compared with 1 to 10% with placebo;[1] children, in particular, may be at a greater risk than adults.[1,2] A retrospective cohort study also found that 48% of adult patients developed decreased serum bicarbonate concentrations while receiving topiramate.[3] Generally, the decreases in serum bicarbonate are mild to moderate and occur soon after starting topiramate. Clinical signs such as hyperventilation may develop.

Some sources such as the US licensed product information recommend that baseline and periodic serum bicarbonate levels should be monitored during topiramate treatment. If metabolic acidosis develops or persists, it may be necessary to reduce the dose or stop topiramate although, in some cases, correcting the acidosis with alkali therapy may be more appropriate.

1. Janssen-Ortho Canada. Important drug safety information: Topamax (topiramate) use is associated with metabolic acidosis (issued 12/01/04). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/topamax_3_hpc-cps-eng.pdf (accessed 01/09/08)
2. Philippi H, *et al.* Topiramate and metabolic acidosis in infants and toddlers. *Epilepsia* 2002; **43:** 744–7.
3. Garris SS, Oles KS. Impact of topiramate on serum bicarbonate concentrations in adults. *Ann Pharmacother* 2005; **39:** 424–6.

Effects on the eyes. There have been rare reports of acute myopia with or without secondary angle-closure glaucoma in adults and children receiving topiramate:[1-3] as of April 2002 the UK CSM was aware of 23 cases worldwide occurring with secondary angle-closure glaucoma.[4] Symptoms include decreased visual acuity and ocular pain which generally appear within one month of starting treatment; hyperaemia and raised intra-ocular pressure may be present with or without mydriasis. Choroidal effusions resulting in anterior displacement of lens and iris have been reported. Appropriate measures to reduce intra-ocular pressure should be taken, and topiramate stopped as rapidly as is clinically feasible.[4] A later review[5] of 115 reports of ocular adverse effects associated with topiramate described 83 cases of bilateral and 3 cases of unilateral acute angle-closure glaucoma; of these, 7 sustained permanent loss of vision. Onset of glaucoma was between 1 and 49 days after starting topiramate therapy, with 85% of cases occurring within the first 2 weeks. Also reported were cases of acute bilateral myopia (17 patients), suprachoroidal effusions (9), scleritis (4), blepharospasm (2), oculogyric crisis (2), and myokymia (1). Diplopia and nystagmus were reported with daily doses of at least 200 to 400 mg topiramate.

1. Gubbay SS. The occurrence of drug-induced myopia as a transient side effect of topiramate. *Epilepsia* 1998; **39:** 451.
2. Sen HA, *et al.* Topiramate-induced acute myopia and retinal striae. *Arch Ophthalmol* 2001; **119:** 775–7.
3. Rhee DJ, *et al.* Bilateral angle-closure glaucoma and ciliary body swelling from topiramate. *Arch Ophthalmol* 2001; **119:** 1721–3.
4. Committee on Safety of Medicines/Medicines Control Agency. Topiramate (Topamax): acute myopia and raised intraocular pressure. *Current Problems* 2002; **28:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
5. Fraunfelder FW, *et al.* Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology* 2004; **111:** 109–11.

Effects on the liver. For reports of hepatotoxicity associated with the addition of topiramate to antiepileptic therapy with carbamazepine or valproate see Interactions, Antiepileptics, on p.474 and p.511 respectively.

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

Effects on the nervous system. Hyperthermia was reported in 10.5% of patients taking topiramate compared with 0.15% of patients taking other antiepileptic drugs in one centre.[1] Children under the age of 6 years, patients on daily doses of 6 mg/kg or more, and those exposed to high ambient temperatures were most at risk. Licensed product information recommends that children should be monitored closely for decreased sweating and hyperthermia, especially during warm or hot weather. Caution is also advised when giving topiramate with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.

Hemiparesis that resolved on withdrawal of topiramate has been reported[2] in 2 patients, although both already had compromised neurological function.

1. Ziad EK, *et al.* Age, dose, and environmental temperature are risk factors for topiramate-related hyperthermia. *Neurology* 2005; **65:** 1139–40.
2. Stephen LJ, *et al.* Transient hemiparesis with topiramate. *BMJ* 1999; **318:** 845.

Effects on sexual function. Topiramate has been associated with sexual dysfunction[1,2] in male and female patients; in all cases symptoms resolved with dosage reduction or withdrawal of the drug.

1. Holtkamp M, *et al.* Erectile dysfunction with topiramate. *Epilepsia* 2005; **46:** 166–7.
2. Sun C, *et al.* Reversible anorgasmia with topiramate therapy for headache: a report of 7 patients. *Headache* 2006; **46:** 1450–3.

Precautions

Topiramate should be used with caution in patients with renal or hepatic impairment. Adequate hydration is recommended to reduce the risk of developing renal calculi, especially in predisposed patients.

Care is required when withdrawing topiramate 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.

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.

◊ References.

1. Bialer M, *et al.* Pharmacokinetic interactions of topiramate. *Clin Pharmacokinet* 2004; **43:** 763–80.

Antiepileptics. In pharmacokinetic studies hepatic enzyme inducers such as *carbamazepine*,[1-3] *phenobarbital*,[2] and *phenytoin*[1,2] were reported to decrease the plasma concentration of topiramate.

For the effect of topiramate on phenytoin and carbamazepine, see p.498 and p.474, respectively. For reports of an increased risk of hepatic impairment in patients taking topiramate with valproate, see p.511.

1. Bourgeois BFD. Drug interaction profile of topiramate. *Epilepsia* 1996; **37:** (suppl 2): S14–S17.
2. Contin M, *et al.* Topiramate therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. *Ther Drug Monit* 2002; **24:** 332–7.
3. Mimrod D, *et al.* A comparative study of the effect of carbamazepine and valproic acid on the pharmacokinetics and metabolic profile of topiramate at steady state in patients with epilepsy. *Epilepsia* 2005; **46:** 1046–54.