



VERDICT & SUMMARY

Tiagabine

(Gabitri[®])

For the treatment of epileptic seizures

Committee's Verdict: **RESTRICTED USE**

BNF: 4.8.1

The clinical diagnosis, initial management and stabilisation of patients with refractory epilepsy are specialist functions. Once patients are stabilised on tiagabine, it is appropriate for GPs to prescribe tiagabine for maintenance use. Patients with epilepsy are expected to receive continuing follow-up in secondary care.

MTRAC updated the review of this drug because relevant NICE guidance had been published.

Licensed indication

Tiagabine is licensed as add-on therapy for partial seizures with or without secondary generalisation in patients with epilepsy where control is not achieved by optimal doses of at least one other antiepileptic drug (AED) in adults and children over 12 years.¹

Background information

Epilepsy is a serious neurological disorder characterised by recurrent, spontaneous seizures. Seizures are classified into two main groups, generalised and partial seizures, according to the area of the brain in which the abnormal discharge originates. If discharge starts in a localised area of the brain, this is called a partial seizure. During a simple partial seizure (SPS) consciousness is unimpaired. If discharge spreads and affects larger areas of the brain, consciousness may be impaired or lost, known as a complex partial seizure (CPS). A secondary generalised seizure (SGS) may develop if the epileptic activity spreads to the entire brain.²

Current treatment options

Most patients will respond to the established antiepileptics, e.g. sodium valproate, phenytoin or carbamazepine, but around 30% often require treatment with more than one AED and may continue to have seizures despite drug treatment.³ Several newer AEDs are available as monotherapy or add-on therapy in patients with refractory epilepsy e.g. vigabatrin, gabapentin, lamotrigine, topiramate, levetiracetam and tiagabine.

Tiagabine is a selective inhibitor of both neuronal and glial gamma-aminobutyric acid (GABA) uptake. This results in increased GABA-mediated inhibition in the brain and reduced neuronal excitability.

Dosage and administration

Dose titration is recommended when initiating tiagabine therapy, starting with 5 mg twice daily, increasing weekly by 5 to 10 mg to a usual maintenance dose of 15 to 30 mg daily given as two divided doses. Patients taking enzyme-inducing AEDs such as phenytoin may require higher maintenance doses of 30 to 45 mg given as three divided doses.

Dosage adjustment is required in patients with mild to moderate hepatic function. Tiagabine should not be used in patients with severe hepatic impairment. As with all AEDs, withdrawal of tiagabine should be gradual over a period of 2 to 3 weeks. Refer to the Summary of Product Characteristics (SPC) for details.¹

Clinical efficacy

Three pivotal, phase III, randomised, double-blind placebo-controlled studies of tiagabine as add-on therapy for partial epilepsy have been published.⁴⁻⁶

Each of the three trials had a baseline period (8-12 weeks) for prospective determination of seizure frequency, followed by randomisation into a double-blind treatment phase (16-22 weeks) to receive placebo (plus usual AEDs) or tiagabine (plus usual AEDs). The doses of tiagabine varied from 4 mg four times daily to 14 mg four times daily.

In two trials the primary outcome was the change in the four-week median CPS frequency during the double-blind phase compared with the baseline phase.^{4,5} In the third trial the primary outcome was responder rate, defined as the number of patients achieving $\geq 50\%$ reduction in four-weekly seizure frequency.⁶

In one trial,⁴ significant reductions, compared with the baseline phase, were observed in the 4-week median CPS frequency with tiagabine 32 mg and 56 mg ($p = 0.03$), but not with 16 mg or placebo. The other trial⁵ found that 8 mg given four times daily produced a significant reduction in 4-week median CPS frequency ($p = 0.02$) but not 16 mg given twice daily or placebo.

Significant reductions, compared with the baseline phase, in the 4-week median SPS frequency were seen with tiagabine 16 mg, 32 mg and 56 mg daily in one trial⁴ ($p \leq 0.04$) and in the second trial, with tiagabine 8 mg given four times daily ($p = 0.008$) but not 16 mg given twice daily or placebo.⁵

Responder rates in the first two trials for CPS and SPS were generally improved in tiagabine-treated patients compared with placebo but the differences only reached significance at some doses.

In the trial by Kalviainen *et al.*,⁶ reduction in frequency of all partial seizures was not statistically different between the tiagabine 10mg three times daily and placebo groups (14% vs. 6%). A significant difference in responder rate for SPS was seen with tiagabine 10 mg given three times daily compared with placebo (21% vs. 6% ($p < 0.01$)).⁶ No significant changes were found in four-week median CPS or SGS frequency or responder rates.⁶

In a cross-over trial⁷ ($n = 88$), patients were randomised to tiagabine (average daily dose 46.4 mg) or placebo after showing a 25% reduction in seizure frequency in response to tiagabine therapy, i.e. they were selected in favour of response to tiagabine. Tiagabine was associated with a significantly greater reduction in the mean weekly partial seizure rates ($p < 0.01$), CPS rates ($p < 0.001$) and secondary generalised tonic-clonic seizure rates ($p < 0.05$) but not for SPS rates, in the double-blind phase when compared with placebo.

Of the 36 tiagabine-treated patients who had results reported, 12 had a $\geq 50\%$ reduction in their weekly partial seizure rate. Likewise 13 of 28 patients with CPS and seven of 21 with SPS demonstrated a 50% responder rate.

Adverse effects

Adverse events accounted for most withdrawals from the pivotal studies,^{4,6} which ranged from 7-11% of patients in the tiagabine groups and 1-2% in the placebo groups. A recent Cochrane review concluded that dizziness, nervousness and tremor were significantly more likely to occur with tiagabine than placebo.⁸ Other adverse events reported in the SPC as occurring more frequently in tiagabine-treated patients were diarrhoea, concentration difficulties, depressed mood, emotional lability and slowness in speech. See SPC for further details.¹

NICE guidance

In March and April 2004, the National Institute for Clinical Excellence (NICE) issued guidance on the use of the newer AEDs for the management of epilepsy in adults and children.^{9,10} NICE recommended the use of monotherapy with older AEDs as first-line treatment. The newer AEDs should be used, within their licensed indications, in those who have not benefited from treatment with older AEDs or for whom these are contraindicated.^{9,10} NICE emphasized the importance of appropriate follow-up arrangements and the use of shared care arrangements where necessary for all people with epilepsy.

Costs

At current prices, one year's treatment costs:

- £317 to £1,425 with tiagabine 10 mg to 45 mg daily
- £636 to £1,866 with levetiracetam 1 g to 3g daily
- £183 to £1,330 with gabapentin 300 mg to 2,400 mg daily

A cost per QALY of approximately £20,000 has been estimated for adjunctive newer AED treatments.¹¹

Conclusions

Tiagabine is an adjunctive antiepileptic drug for the treatment of partial seizures with or without secondary generalisation.

Clinical trials have shown tiagabine to be an effective adjunctive treatment for reducing partial seizure rates in epileptic patients. However, since the earlier MTRAC verdict in 2000, no data on comparative trials with other add-on anti-epileptic therapies have been published. Thus the place for tiagabine is still unclear. NICE recommends that tiagabine can be considered as one of the AEDs to be added after monotherapy has been tried, if treatment with the older AEDs is inappropriate.

References

1. Cephalon UK Ltd. Gabitril 5mg, Gabitril 10mg, Gabitril 15mg. *Summary of Product Characteristics* 2002.
2. Sisodiya S, Duncan J. Epilepsy: epidemiology, clinical assessment, investigation and natural history. *Medicine* 2004;**32**:47-56.
3. LaRoche SM, Helmers SL. The new antiepileptic drugs. *JAMA* 2004;**291**:605-14.
4. Uthman BM, Rowan AJ, Ahmann PA *et al.* Tiagabine for complex partial seizures. *Arch Neurol* 1998;**55**:56-62.
5. Sachdeo RC, Leroy RF, Krauss GL *et al.* Tiagabine therapy for complex partial seizures: A dose-frequency study. *Arch Neurol* 1997;**54**:595-601.
6. Kalviainen R, Brodie MJ, Duncan J *et al.* A double-blind, placebo-controlled trial of tiagabine given three-times daily as add-on therapy for refractory partial seizures. *Epilepsy Research* 1998;**30**:31-40.
7. Crawford P, Meinardi H, Brown S *et al.* Tiagabine: Efficacy and safety in adjunctive treatment of partial seizures. *Epilepsia* 2001;**42**:531-8.
8. Pereira J, Marson AG, Hutton JL. Tiagabine add-on for drug-resistant partial epilepsy (Review). *The Cochrane Library* 2005;**1**:1-22.
9. National Institute for Clinical Excellence. Newer drugs for epilepsy in adults. Technology Appraisal Guidance 76. 2004.
10. National Institute for Clinical Excellence. Newer drugs for epilepsy in children. Technology Appraisal Guidance 79. 2004.
11. Wilby J, Kainth A, Hawkins N *et al.* Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. *Health Technol Assess* 2005;**9**:1-829.

Launch date: November 2000

Manufacturer: Cephalon UK Ltd

PL 16260/009-11

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

MTRAC can be contacted at the Dept. of Medicines Management, Keele University, Keele, Staffs ST5 5BG
Tel: 01782 584131 Fax: 01782 713586 Email: mtrac@keele.ac.uk Web: www.mtrac.co.uk

(THIS VERDICT SHEET REPLACES VS06/00)

Date: June 2005

©Midlands Therapeutics Review & Advisory Committee

VS05/08



KEELE
UNIVERSITY

Faculty of health



Department of

medicines management

