AUSTRALIAN PRODUCT INFORMATION – GABITRIL® (TIAGABINE HYDROCHLORIDE MONOHYDRATE) TABLETS

1 NAME OF THE MEDICINE

Tiagabine hydrochloride monohydrate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tiagabine hydrochloride monohydrate has an asymmetric centre. GABITRIL contains only the R(-)-enantiomer named (R)-N-(4,4)-di(3-methylthien-2-yl)-but-3-enyl) nipecotic acid, hydrochloride monohydrate. It is a white to off-white crystalline powder and is sparingly soluble in water (22 mg/mL), soluble in ethanol and practically insoluble in non-polar solvents such as diethyl ether. For the carboxylic acid moiety pKa = 3.3; for the amine pKa = 9.4.

GABITRIL is an antiepileptic drug. The active ingredient is tiagabine, present as tiagabine hydrochloride monohydrate. Contains lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

GABITRIL 5 mg tablets are white, round, biconvex film-coated tablets (marked 251). Each 5 mg tablet contains tiagabine 5 mg in the form of tiagabine hydrochloride monohydrate

GABITRIL 10 mg tablets are white, oval, biconvex film-coated tablets (marked 252). Each 10 mg tablet contains tiagabine 10 mg in the form of tiagabine hydrochloride monohydrate.

GABITRIL 15 mg tablets are white, oval, biconvex film-coated tablets (marked 253). Each 15 mg tablet contains tiagabine 15 mg in the form of tiagabine hydrochloride monohydrate.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of partial seizures, as add on therapy in patients who are not controlled satisfactorily with other antiepileptic drug(s).

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children over 12 years

GABITRIL should be taken with meals in three daily doses. For optimal results the dose of GABITRIL should be titrated for each patient as follows. The initial dosage is 7.5-15 mg daily, followed by weekly increments of 5-15 mg daily. The usual maintenance dose is in the range of 30-50 mg daily within which

a clear dose-response is seen. Doses up to 70 mg daily have been well tolerated. In patients who are not taking enzyme-inducing drugs, the maintenance dose should initially be 15-30 mg/day. Adjustment of the maintenance tiagabine dosage should be considered when adding or stopping other anti-epileptic drugs. Although there is no evidence of withdrawal seizures with GABITRIL, it is recommended to taper off treatment over a period of 2-3 weeks (see **Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Children under 12 years

Safety and effectiveness in children below the age of 12 years have not been established. Therefore, the drug should not be used in children under 12 years.

Use in elderly

Tiagabine should be used with caution in this age group (see **Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Use in patients with mild to moderate hepatic impairment

Tiagabine is metabolised in the liver and since the pharmacokinetics of tiagabine with mild to moderate impaired liver function is modified, the GABITRIL dosage should be adjusted by reducing the individual doses and/or prolonging the dose interval.

4.3 CONTRAINDICATIONS

GABITRIL should not be used in case of:

- Known hypersensitivity to tiagabine or any of the tablet components
- Severely impaired liver function
- Combination with St John Wort (hypericum perforatum).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

It is important to follow the recommended rate of dosage titration with GABITRIL (see **section 4.2, DOSE AND METHOD OF ADMINISTRATION**) in order to minimise the potential for adverse events to tiagabine which may result from a too rapid increment in dosage during the titration period. The dose of GABITRIL which has been tailored to the patient's needs will be better tolerated.

In view of the GABAergic mode of action of tiagabine and the data from animal studies, a risk of aggravation of absences in patients with generalized epilepsy treated with tiagabine cannot be excluded.

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency or the onset of new types of seizures with tiagabine. These phenomena may be the consequence of an overdosage, a decrease in plasma concentrations of concomitant antiepileptic treatment, a progress of the disease, or a paradoxical effect.

Non-convulsive status epilepticus (paradoxical) has been reported with tiagabine in a relatively-resistant population requiring add-on therapy, particularly during dose titration. The dose should be carefully titrated to reduce the risk of paradoxical seizure-like activity. Should non-convulsive status epilepticus occur, reduction or cessation of the dose of tiagabine should be considered.

Although there is no evidence of withdrawal seizures with GABITRIL it is recommended to taper off treatment over 2-3 weeks (see **section 4.2, DOSE AND METHOD OF ADMINISTRATION**).

In patients with a history of serious behavioural problems including generalised anxiety and depression, there is a risk of recurrence of these symptoms during GABITRIL treatment. Treatment with GABITRIL should therefore be initiated with low doses and patients observed carefully.*

Rare cases of visual field defects have been reported with tiagabine. Some patients were asymptomatic. If visual symptoms develop, or if a field defect is suspected, the patient should be referred to an ophthalmologist for further evaluation including perimetry.*

Spontaneous bruising has been reported. If such bruising is observed, full blood count, including platelets, should be performed.

Serious rash, including vesiculobullous rash has occurred in patients receiving GABITRIL.

Seizures in Patients Without Epilepsy: Post marketing reports have shown that GABITRIL has been associated with new onset seizures and status epilepticus in patients without epilepsy. Dose may be an important predisposing factor in the development of seizures, although seizures have been reported in patients taking doses of GABITRIL as low as 4 mg/day. In most cases, patients were using concomitant medications (antidepressants, antipsychotics, stimulants, opioids) that are thought to lower the seizure threshold. Some seizures occurred near the time of a dose increase, even after periods of prior stable dosing. The safety and efficacy of GABITRIL have not been established for any indication other than the treatment of partial seizures, as add on therapy in patients who are not controlled satisfactorily with other antiepileptic drugs. In non-epileptic patients who develop seizures while taking GABITRIL treatment should be discontinued and patients should be evaluated for an underlying seizure disorder. Seizures and status epilepticus are known to occur with GABITRIL overdosage (see **section 4.9, OVERDOSE**).

Suicidal Behaviour and Ideation

Antiepileptic drugs, including tiagabine hydrochloride monohydrate, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED- treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in the placebo-treated patients, but the number is too small to allow any conclusions about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with the AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo patients with events/1000 patients	Drug patients with events/1000 patients	Relative Risk: Incidence of events in Drug patients/incidence in Placebo patients	Risk Difference: Additional Drug patients with events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing tiagabine hydrochloride monohydrate or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Use in hepatic impairment

Tiagabine is metabolised in the liver. The pharmacokinetics of tiagabine in patients with mild to moderate impaired liver function is modified (see **section 4.2, DOSE AND METHOD OF ADMINISTRATION**).

Use in the elderly

The pharmacokinetic properties of tiagabine do not seem to be significantly modified in the elderly. However, only limited information is available on the use of GABITRIL in elderly patients. It is therefore recommended to use tiagabine with caution in this age group.

Paediatric use

Safety and effectiveness in children below the age of 12 years have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Findings from a series of pharmacokinetic interaction studies support the conclusion that tiagabine does not have any clinically significant effect on the plasma concentrations of phenytoin, carbamazepine, phenobarbitone, valproate, warfarin, digoxin, theophylline and hormones used in oral contraceptives.

However anti-epileptic drugs which induce hepatic enzymes (e.g. phenytoin, carbamazepine, phenobarbitone and primidone) enhance the metabolism of tiagabine. The plasma concentration of tiagabine may be reduced by a factor of 1.5-3 by concomitant use of these drugs.

The combination of tiagabine with St John Wort (hypericum perforatum) may lead to lower exposure and loss of efficacy of tiagabine, due to the potent induction of CYP3A4 by St John Wort (increasing tiagabine metabolism). Therefore, the combination of tiagabine with St John's Wort is contraindicated (see **section 4.3, CONTRAINDICATIONS**).

Cimetidine does not have a clinically significant effect on tiagabine plasma levels. Although tiagabine may slightly prolong the CNS depressant effect of triazolam, the interaction is unlikely to be relevant to clinical practice. Formal interaction studies with other benzodiazepines have not been conducted, however clinically relevant interactions were not noted in the clinical trials.

In-vitro data showed that tiagabine is 96% bound to human plasma protein and therefore has the potential to interact with other highly protein bound compounds. Such an interaction can potentially lead to higher free fractions of either tiagabine or the competing drug.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In rats where both sexes were treated with tiagabine, post-implantation loss was increased. Following maternal treatment at 100 mg/kg/day, male pups had reduced body weight up to 21 weeks of age. After 12 months treatment of beagle dogs with tiagabine, ovarian and uterine weights were significantly reduced

Use in pregnancy

Category B3.

Risk associated with epilepsy and antiepileptics

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of foetal abnormalities;

- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Risk associated with tiagabine

Clinical experience of the use of GABITRIL in pregnant women is limited. Studies in rats revealed that tiagabine and/or its metabolites crossed the placenta and were distributed in foetal tissue. Foetotoxicity and foetal abnormalities occurred at the maternotoxic dose. Pup birth weight and early postnatal survival was reduced in offspring of rats dosed with tiagabine 100 mg/kg/day from late gestation to weaning. In rabbits post-implantation loss, foetal abnormalities, delayed ossification, reduced foetal viability and body weight occurred.

Use in lactation.

As there is no information on the use of tiagabine during lactation, GABITRIL should only be used during breast-feeding if the potential benefit outweighs the possible risks. Studies with C^{14}-tiagabine indicated that tiagabine and/or its metabolites were found in the breast milk of rats after a single oral dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with other antiepileptic drugs, caution should be shown when driving or operating machinery whilst on treatment with tiagabine.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

The table below (table 2) presents the adverse events experienced by at least 5% of the tiagabine treated patients in the 3 double-blind, parallel, placebo-controlled studies (TIA 106, TIA 107 and TIA 109). The treatment duration in these studies was 16-22 weeks. The parallel, placebo-controlled studies allow a direct comparison of frequencies of adverse events between tiagabine and placebo.

Table 2: Adverse events experienced in parallel, placebo controlled studies in at least 5% of the patients treated with tiagabine.

	Tiagabine N=493 %	**Placebo** N=276 %
Body as a whole		
Accidental injury	17	20
Infection	15	16
Flu syndrome	9	7
Abdominal pain	8	3
Pain	6	3
Digestive system		
Nausea	12	9
Vomiting	8	5
Diarrhoea	8	3
Nervous system		
Dizziness	29	16
Tiredness	22	15
Somnolence	19	16
Headache	15	15
Nervousness (non-specific)	11	4
Tremor	10	4
Insomnia	6	4
Concentration Difficulties (Thinking abnormal)	6	3
Ataxia	6	3
Confusion	5	3
Respiratory System		
Pharyngitis	8	4
Rhinitis	8	5
Skin and Appendages		
Rash	6	4
Special Senses		
Amblyopia	5	5
Diplopia	5	8

Adverse events are generally mild to moderate. Most events occur during the titration phase and are often transient. The most commonly observed adverse events associated with the use of tiagabine in all placebo controlled clinical trials and which occur less frequently in patients treated with placebo are: dizziness, tiredness, somnolence*, unspecific nervousness, tremor, difficulty in concentrating, diarrhoea, depressed mood (less than 5%) and emotional lability (less than 5%).

POST MARKETING EXPERIENCE

Rare cases of seizures, non-convulsive status epilepticus (see **section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE**), slow-down EEG, encephalopathy, confusion, agitation, psychotic reactions (hallucination and delusion), bruising have been reported in association with tiagabine therapy. The occurrence of seizures was confounded by other antiepileptic drugs and the underlying condition.

Rare cases of visual field defects have been reported including quadrantanopia, hemianopia and concentric field defects. Relationship to tiagabine was uncertain and, in some cases, confounded by other neurological conditions and the use of other antiepileptic drugs (see **section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Additional adverse events that have been reported with the use of GABITRIL include: blurred vision, vomiting, ataxia, muscle twitching, abnormal gait, speech disorder, hostility, insomnia, bullous dermatitis, exfoliative dermatitis, vesiculobullous rash.

Isolated cases of thrombocytopenia have been reported in the context of associated viral infections and other antiepileptics.

Very rare cases of abnormal hepatic function (elevated SGPT, GGT) have been reported. Causation to tiagabine has not been definitely established. Seizures including status epilepticus in patients without epilepsy.

4.9 OVERDOSE

Human experiences of acute overdose with GABITRIL is limited. Eleven patients in clinical trials took single doses of GABITRIL up to 800 mg. All patients fully recovered usually within one day. The most common symptoms reported after overdose included somnolence, impaired consciousness, agitation, confusion, speech difficulty, hostility, depression, weakness and myoclonus. One patient who ingested a single dose of 400 mg experienced tonic-clonic status epilepticus, which responded to intravenous phenobarbitol.

From post-marketing experience, there have been no reports of fatal overdose involving GABITRIL alone (doses up to 720 mg), although a number of patients required intubation and ventilatory support as part of the management of their status epilepticus. Overdoses involving multiple drugs, including GABITRIL, have resulted in fatal outcomes.

Symptoms

Symptoms most often accompanying GABITRIL overdose, alone or in combination with other drugs, have included seizures, including status epilepticus in patients with and without underlying seizure disorders, mute and withdrawn appearance of the patient, respiratory arrest, nonconvulsive status epilepticus, coma, loss of consciousness, ataxia, dizziness, encephalopathy, amnesia, confusional state, somnolence, dyskinesia, drowsiness, impaired speech, headache, psychotic disorder, agitation, lethargy, myoclonus, spike wave stupor, tremors, disorientation, vomiting, hostility, aggression, temporary paralysis and urinary incontinence. Respiratory depression was seen in a number of patients, including children, in the context of seizures.

Treatment

There is no specific antidote for overdose with GABITRIL. If indicated, elimination of unabsorbed drug should be achieved by activated charcoal. General supportive care of the patient is indicated including monitoring of vital signs and observation of clinical status of the patient. Since tiagabine is mostly metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tiagabine is a potent and selective inhibitor of both neuronal and glial GABA (γ-amino-butyric acid) uptake, resulting in an increase in GABAergic mediated inhibition in the brain. Tiagabine lacks significant affinity for other neurotransmitter receptor binding sites and/or uptake sites.

Clinical trials

The efficacy of tiagabine as add-on therapy has been evaluated in 2 cross-over (non-pivotal) and 3 parallel (pivotal) trials in a total of 1032 patients, of whom 675 received GABITRIL.

Doses in clinical trials are expressed as tiagabine hydrochloride anhydrous. Doses recommended in the section "**DOSE AND METHOD OF ADMINISTRATION" (section 4.2)** are expressed as tiagabine (which is equivalent to 0.91 times that of tiagabine hydrochloride anhydrous).

Cross-over trials

The trials consisted of an initial screening period in which the dose was raised until a response or adverse events developed. Thereafter a 4-week fixed dose period followed. The patients who responded during the fixed dose period were randomised to the double-blind, cross-over period of 23 weeks duration.

A total of 182 patients entered these trials and 78 entered the cross-over phase. These two trials gave supportive evidence for the efficacy of GABITRIL in the treatment of partial and secondary generalised seizures.

Parallel Trials

The parallel trials each included a placebo arm and investigated differing doses (TIA-106) or regimens (TIA-107, TIA-109). The parallel trials had an 8 or 12 week baseline period, then a double-blind period with a titration period of 4-6 weeks, followed by an 8-12 week fixed dose assessment period and a 4 week termination period.

A total of 850 patients were enrolled, 769 randomised, 493 of whom received tiagabine. Ages ranged from 12-77 years. Tiagabine treatment was added to existing antiepileptic medication including 1-3 anti-epileptic drugs.

TIA 106 – Dose Finding Trial

Patients were randomised to treatment with placebo (n=91), 16 mg tiagabine HCl daily (4 mg qid, n=61), 32 mg tiagabine HCl daily (8 mg qid, n=88) or 56 mg tiagabine HCl daily (14 mg qid, n=57). 295 patients were assessable for efficacy.

The primary efficacy outcome measure was the change from baseline in 4-week complex partial seizure rates for the combined (32 mg + 56 mg) group. A significant decrease in the primary endpoint, complex partial seizure rate was seen in this tiagabine treatment group compared with placebo. A significant decrease in 4-week seizure rate was also seen for combined partial and simple partial and secondary generalised tonic clonic seizures. In addition, the other secondary outcome measure of percentage of patients achieving ≥ 50% seizure reduction for the (32 mg + 56 mg) tiagabine treatment group was in the

range of 24 - 44% for the different seizure types and was statistically significant over placebo for complex partial, simple partial and all partial seizure types.

Tiagabine HCl as add-on therapy was shown to be effective in the treatment of partial seizures at doses of 32 mg and 56 mg/day, with some efficacy at 16 mg/day in some patients.

TIA 107 - Dose frequency study (tid)

This trial examined three times daily dosing with 30 mg tiagabine HCl given as three 10 mg doses. 77 patients were randomised to tiagabine and 77 to placebo and all were included in the intent-to-treat analysis.

The primary endpoint of the study was the proportion of responders, that is the percentage of patients achieving a reduction of 50% or more in 4-weekly seizure rate for partial seizures compared to baseline. There was no significant difference from placebo in the proportion of responders for partial seizures overall, although the secondary endpoint of median reduction in 4-weekly seizure rates, was significantly better than placebo. However for simple partial seizures there was a significant improvement in the proportion of responders and the median reduction in 4-weekly seizure rate in the tiagabine treatment group compared with placebo.

TIA 109 - Dose frequency study (bid vs. qid)

This trial compared a dose of 32 mg daily given as 16 mg bid or as 8 mg qid with placebo as add-on therapy for complex partial seizures. 108 patients received placebo, 106 received tiagabine HCl 16 mg bid and 104 patients received tiagabine HCl 8 mg qid.

The primary efficacy measure was the change from baseline in 4 week complex partial seizure rates compared with placebo. Patients treated with tiagabine HCl 16 mg bid and 8 mg qid experienced fewer complex partial seizures per 4 weeks compared to placebo. The frequency of patients with $\geq$50% reduction in 4-week complex partial seizure rates were significantly higher in each of the 2 tiagabine groups compared to placebo. Approximately 20 - 30% of patients treated with tiagabine had at least a 50% reduction in complex partial and combined partial seizures.

The results of the pivotal parallel trials are tabulated below:

Table 3: Dose-range parallel-group study: efficacy results (from the Clinical Summary)

	TIA-106 Placebo	TIA-106 Tiagabine 16 mg	TIA-106 Tiagabine 32 mg	TIA-106 Tiagabine 56 mg	TIA-107 Placebo	TIA-107 Tiagabine 10 mg tid	TIA-109 Placebo	TIA-109 Tiagabine 16 mg bid	TIA-109 Tiagabine 8 mg qid
All Partial Seizures Number of patients	90	61	86	55	77	77	106	106	102
Median reduction in 4-weekly seizure rate	4%	12% (ns)	24% *	37% *	0%	13% *	5%	19% (ns)	12% (ns)
Proportion of responders (95% confidence interval)	4% 0%-8%	10% (ns) 2%-18%	20% * 12%-26%	31% * 19%-43%	6% 1%-11%	14% (ns) 6%-20%	8% 3%-13%	28% * 19%-37%	23% * 15%-31%
Complex Partial Seizures Number of patients	90	61	86	55	75	73	106	106	102
Median reduction in 4-weekly seizure rate	11%	13% (ns)	25% *	33% *	0%	6% (ns)	3%	21% (ns)	15% *
Proportion of responders (95% confidence interval)	4% 0%-8%	8% 1%-15%	20% * 12%-28%	29% * 17%-41%	15% 7%-23%	21% (ns) 12%-30%	10% 4%-16%	30% * 21%-39%	27% * 18%-36%
Simple Partial Seizures Number of patients	49	37	49	31	50	53	49	57	42
Median reduction in 4-weekly seizure rate	-6%	31% *	30% (ns)	47% *	0%	13% *	-6%	26% (ns)	12% *
Proportion of responders (95% confidence interval)	10% 2%-18%	30% * 15%-45%	35% * 22%-48%	39% * 22%-56%	6% -1%-13%	21% * 10%-32%	16% 6%-26%	37% * 24%-50%	29% (ns) 15%-43%
Secondary Generalised Tonic-Clonic Seizures Number of patients	32	24	27	23	35	38	30	43	43
Median reduction in 4-weekly seizure rate	9%	53% *	31% (ns)	43% (ns)	0%	22% (ns)	16%	37% (ns)	49% (ns)
Proportion of responders (95% confidence interval	31% 15%-47%	54% (ns) 34%-74%	41% (ns) 22%-60%	48% (ns) 28%-68%	26% 11%-41%	32% (ns) 17%-47%	32% 15%-49%	42% (ns) 27%-57%	47% (ns) 32%-62%

NOTE: * Indicates statistical significance in favour of tiagabine over placebo at the 5% level; (ns) indicates lack of statistical significance at the 5% level.

Summary

The trials showed that tiagabine is efficacious in doses above 30 mg/day (with some efficacy at 16 mg/day) in the treatment of partial (simple and complex) and showed a tendency to efficacy for secondary generalised seizures. There was a trend towards better tolerance with a tid or qid dose regimen.

Monotherapy

The experience with tiagabine monotherapy is still limited.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Tiagabine is rapidly and virtually completely absorbed from GABITRIL tablets with an absolute bioavailability of 80 to 90%. Administration of GABITRIL with food results in a decreased rate, but not extent, of absorption. Within the therapeutic range, there is a linear relationship between the dose and extent of absorption and elimination of tiagabine.

Distribution

The volume of distribution of tiagabine is approximately 1 L/kg and plasma protein binding is about 96%.

Metabolism

Tiagabine is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP3A, with renal clearance being negligible. Less than 2% is excreted unchanged in the urine and faeces. No active metabolites have been identified. In epilepsy clinical trials, most patients were receiving hepatic enzyme-inducing agents (e.g. carbamezapine, phenytoin, primidone and phenobarbitol). The pharmacokinetic profile in induced patients is significantly different from the non-induced population. The systemic clearance of tiagabine in induced patients is approximately 60% greater resulting in considerably lower plasma concentrations and an elimination half-life ($t_{1/2}$) of 2 to 5 hours. Given this difference in clearance, the systemic exposure after a dose of 32 mg/day in an induced population is expected to be comparable to the systemic exposure after a dose of 12 mg/day in a non-induced population. Similarly, the systemic exposure after a dose of 56 mg/day in an induced population is expected to be comparable to the systemic exposure after a dose of 22 mg/day in a non-induced population.

There is no evidence that tiagabine causes induction or inhibition of hepatic drug metabolising enzymes. In patients with mild to moderate hepatic impairment, the elimination half-life of tiagabine is increased to 12-16 hours. Therefore these patients may require a reduction in dose.

There seems to be no difference in the pharmacokinetic profile of tiagabine in the elderly (>65 years) and young adults.

Excretion

The elimination half-life ($t_{1/2}$) of tiagabine is 7 to 9 hours in normal volunteers.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The results of a wide range of mutagenicity tests showed that tiagabine is unlikely to be genotoxic to humans.

Carcinogenicity

In long-term (2-year) carcinogenicity studies conducted in the rat and mouse, only the rat study revealed increased incidences of hepatocellular adenomas in females at 200 mg/kg/day (72 times the maximum anticipated clinical exposure based on plasma AUC) and benign Leydig cell tumours in males at 200 mg/kg/day (39 times the maximum anticipated clinical exposure).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are colloidal anhydrous silica, microcrystalline cellulose, ascorbic acid, lactose, pregelatinised maize starch, crospovidone, hydrogenated vegetable oil, stearic acid, magnesium stearate, hypromellose, hyprolose and titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. Refer to **Section 4.5, INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS** for further information.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

GABITRIL 5 mg tablets are supplied in white HDPE bottles with a tamper proof cap of 50 tablets.
GABITRIL 10 mg tablets are supplied in white HDPE bottles with a tamper proof cap of 50 tablets
GABITRIL 15 mg tablets are supplied in white HDPE bottles with a tamper proof cap of 50 tablets

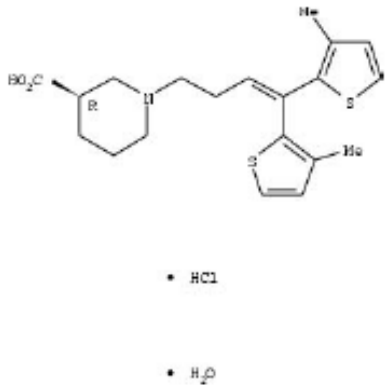
(Note: Not all strengths or pack sizes may be available in Australia.)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

CAS No. 145821-57-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 Prescription Only Medicine

8. SPONSOR

Teva Pharma Australia Pty Limited
37 Epping Rd
Macquarie Park, NSW, 2113
1800 288 382
www.tevapharma.com.au

9. DATE OF FIRST APPROVAL

14/09/2006

10. DATE OF REVISION

18 May 2018

GABITRIL® is a registered trade mark of Novo Nordisk A/S, used under licence by Teva Pharma Australia Pty Limited.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Nature and contents of container section now contains information previously located in Pharmaceutical Form (Section 3).
8	Change of Sponsor and consequential editorial changes