Scottish Medicines Consortium

zonisamide hard capsules 25 mg, 50 mg, 100 mg (Zonegran®)
Eisai Ltd (No. 216/05)

4 November 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Zonisamide (Zonegran®) is accepted for restricted use within NHS Scotland as adjunctive therapy in adult patients with partial seizures, with or without secondary generalisation.

It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy and should be used principally in patients who have not benefited from treatment with an older anti-convulsant drug such as carbamazepine or sodium valproate, or for whom these drugs are unsuitable because of contra-indications, interaction or poor tolerance.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

zonisamide 25mg, 50mg, 100mg hard capsules (Zonegran®)

Indication

Adjunctive therapy in the treatment of adult patients with partial seizures with or without secondary generalisation.

Dosing information

Zonisamide must be added to existing therapy and the dose should be titrated on the basis of clinical effect from 50 mg in two divided doses increased at one-weekly intervals in 100 mg/day increments. Doses of 300 mg/day to 500 mg/day have been shown to be effective, though some patients may respond to lower doses, especially if not taking agents which induce the metabolism of zonisamide through the CYP3A4 system.

Zonisamide can be administered once or twice daily after the titration phase.

UK launch date

June 2005

Comparator medications

There were no trials conducted with suitable comparator medicines although several are licensed for this indication.

Cost of relevant comparators

The table below gives costs for medicines which are licensed as adjunctive therapy in partial seizures with or without generalisation. Note that some anti-epileptic drugs (AEDs) are licensed both as monotherapy and as adjunctive therapy (e.g. lamotrigine, topiramate, oxcarbazepine) and that many other AEDs can be used in combination therapy. Thus, for example, if a patient is not responding to two or three agents the treatment options are not restricted to adjunctive therapy.

For consistency between individual agents, they have been costed at their maximum recommended dose as adjunctive therapy, however all are subject to dose titration on the basis of efficacy and tolerability and the actual doses used are likely to be below the maximum. For zonisamide and levetiracetam, costs are also given for the doses used in the base case economic analysis included with the submission.

Agent	Maximum dose	Cost per annum
Zonisamide (Zonegran®)	**250 mg twice daily** **150 mg twice daily**	**£2038** **£1223**
Gabapentin (Neurontin®)	800 mg three times a day	£1499
Pregabalin (Lyrica®)	300mg twice daily or 200mg three times daily	£837 £1256
Lamotrigine (non-proprietary) with valproate without valproate	 200 mg daily 400 mg daily	 £595 £1191
Levetiracetam (Keppra®)	1.5g twice daily 1.0g twice daily	£2162 £1269
Oxcarbazepine (Trileptal®)	1.2 g twice daily	£1165
Tiagabine (Gabitril®)	15 mg three times daily	£1421
Topiramate (Topamax®)	400 mg twice daily	£2901
Vigabatrin (Sabril®)+	1.5g twice daily	£674

+ Vigabatrin should only be used when all other combinations are inadequate or are not tolerated.

Summary of evidence on comparative efficacy

Partial epilepsy originates in a localised part of the brain but may be associated with more generalised seizures. Simple partial (SP) seizures are not associated with impairment of consciousness, while complex partial (CP) seizures are acccompanied by such impairment and are often more disabling. The mechanism of zonisamide in suppressing partial seizures is not entirely clear, but it reduces the spread of seizure discharges and disrupts subsequent epileptic activity.

Only one trial was considered by the European Medicines Agency (EMEA) to be of sufficient duration to assess the efficacy of zonisamide in this indication. It recruited patients aged ≥12 years with partial seizures, with or without secondary generalisation, who were unsatisfactorally controlled despite a stable regimen of 1-3 AEDs. Patients maintained seizure diaries throughout the study, including a 12-week baseline period. Those with ≥12 partial seizures and no more than a 3-week seizure-free period during baseline were randomised to receive adjunctive therapy with placebo or zonisamide 100 mg, 300 mg or 500 mg daily in the ratio 2:1:1:2 respectively.

Following randomisation, patients entered a 6-week dose titration period followed by an 18-week fixed dose assessment period. An intention-to-treat (ITT) population consisted of all randomised subjects who had had at least one dose of study medication and had post-baseline data on partial seizure frequency (n=347). However, the primary efficacy analysis included patients in the ITT group who also had partial seizure frequency data recorded during the fixed-dose assessment period on weeks 19-36 (n=312).

There were two primary end-points:

(i) The median percentage change from baseline in the frequency of CP seizures without secondary generalisation was normalised to a 28-day period and analysed using an analysis of variance (ANOVA) model on rank-transformed data with the main effects of treatment and

study centre. A step-down procedure was used to compare each active treatment with placebo, starting with zonisamide 500 mg/day. Medians were compared by the Hodges Lehman test.

(ii) The percentage of responders, where response was defined as ≥50% reduction in the frequency of CP seizures from baseline, was compared between the zonisamide 500 mg/day and placebo using the Cochran-Mantel-Haenszel test with treatment centre as the stratification variable.

At baseline, the mean historic seizure frequency, normalised to a 28-day period, ranged from 9.6 to 13 for CP seizures, and 9.2 to 12 for SP seizures. Median values were generally much lower, e.g. 2.9 to 6.3 for CP seizures. For the primary efficacy population, there was a significant advantage over placebo for zonisamide 500 mg in terms of the median percentage change in CP seizure frequency from baseline and the percentage of responders. For the former outcome, the treatment difference was 31% (95% confidence intervals 16%, 45% $p<0.0001$) and for the percentage of responders the odds ratio was 4.1 (1.9, 8.6 $p<0.001$).

In the sequential analysis of reduction in CP seizure frequency, the difference from placebo was not significant for the 300 mg/day zonisamide group and not analysed for the 100 mg/day group. There was no statistical testing of the differences in response rates for those groups.

Change in seizure frequency and response rates were analysed in a similar manner for all partial seizures and all seizures. In all cases, there was a significant advantage over placebo for zonisamide 500 mg/day. The decrease in seizure frequency was significantly in favour of the 300 mg/day groups for all partial seizures and all seizures but there were no significant differences for the 100 mg/day group.

Patients experienced a median increase of around 3.0 seizure-free days per 28 days with the 300 mg/day and 500 mg/day doses of zonisamide, while the increase with 100 mg/day was similar to placebo (1.3 and 1.2 seizure-free days/28 days respectively).

The results in the primary efficacy population were supported by the ITT analysis and by results from a more narrowly defined efficacy population.

Summary of evidence on comparative safety

Treatment-related adverse events were reported for 61% of patients assigned to zonisamide in placebo-controlled studies compared with 49% for placebo. They led to discontinuation in 19% and 8.6% of patients respectively, and were serious in 2.2% and 0.9% of patients. The most common adverse events with zonisamide were those affecting the central nervous system, particularly somnolence which was more common in the titration phase than the steady-state dosing phase of trials. Zonisamide has been associated with the development of renal calculi and, though this is uncommon, precautions such as increasing fluid input and urine output are advised in the Summary of Product Characteristics.

Summary of clinical effectiveness issues

In general, the groups in the main trial were well matched, however patients in the zonisamide 300 mg/day group were younger than those in the other groups, had a shorter median time since epilepsy diagnosis, a substantially lower historic CP seizure frequency and a higher SP seizure frequency compared with other groups.

Zonisamide is licensed for partial seizures with or without generalisation but the primary end-point in the main trial was CP without generalisation. Secondary end-points included analysis of frequency and response rates for all partial seizures (without generalisation) and all seizures irrespective of type, including non-partial seizures. None of these end-points correspond exactly to the licensed indication.

Zonisamide has not been compared in trials with competitor products for this indication therefore evidence is restricted to placebo-controlled trials.

Summary of comparative health economic evidence

The manufacturer submitted a cost utility model comparing zonisamide 300mg as first choice add-on followed by lamotrigine 300mg vs. levetiracetam 2000 mg followed by lamotrigine 300mg.

The analysis used clinical trial data, resources as advised by Scottish experts, valid sources to cost these and adopted the same utility values as those used in the recent NICE Technology Appraisal. After 15 years both arms had virtually the same costs and QALYs. Sensitivity analyses showed this result was reasonably robust to wide changes in costs and clinical effectiveness rates for the two AEDs.

The main issue with the model is that one comparator was chosen, the 300mg dose regimen was used and the order of drug treatment and the switching trigger may not represent clinical practice.

In conclusion, although there were some concerns, the analyses indicated that zonisamide 300 mg is likely to be as cost effective as levetiracetam 2000mg when used as adjunctive therapy.

Patient and public involvement

Patient Interest Group Submission: Epilepsy Scotland

Budget impact

The manufacturer estimates a gross cost of drug £52k in year 1 rising to £814k in year 5 and this should be offset by displacement of sales of levetiracetam, giving no significant net additional costs. This assumes that only the 300 mg dose of zonisamide will be used.

Guidelines and protocols

General guidance on the treatment of epilepsy, including pharmacological treatment, is available from a number of sources including the National Institute for Clinical Excellence (Clinical Guideline 20, October 2004) and the Scottish Intercollegiate Guidelines Network (Guideline No.70, April 2003). Neither gives specific advice on the treatment of partial seizures.

Additional information

On December 10th 2004, following a full submission, the Scottish Medicines Consortium issued the following advice

Pregabalin (Lyrica®) is accepted for restricted use within NHS Scotland as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy and should be used principally in patients who have not benefited from treatment with an older anti-convulsant drug such as carbamazepine or sodium valproate, or for whom these drugs are unsuitable because of contra-indications, interaction or poor tolerance.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 13 October 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Brodie MJ, Duncan R, Vespignani H, Solyom A, Bitenskyy V, Lucas C. Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures. Epilepsia 2005;46:31–41.

European Medicines Agency. Zonegran. Scientific Discussion www.emea.eu.int/ accessed August 2005

Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults. National clinical guideline No. 70 April 2003. www.sign.ac.uk//index.html accessed August 2005

National Institute for Clinical Excellence. The epilepsies. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. Clinical Guideline 20. October 2004. www.nice.org.uk/ accessed August 2005

National Institute for Clinical Excellence. Newer drugs for epilepsy in adults. Technology Appraisal 76. March 2004. www.nice.org.uk/ accessed August 2005