Committee’s Verdict: CATEGORY B (Q3)

**Initiation and stabilisation of treatment with zonisamide should be the responsibility of the specialist. It is then appropriate for GPs to prescribe zonisamide for maintenance with the guidance of a shared care agreement. Patients with epilepsy are expected to receive continuing follow-up in secondary care.**

**Category B:** suitable for restricted prescribing under defined conditions

**Q3 rating:** The evidence for the efficacy of zonisamide for the adjunctive treatment of partial seizures was considered to be relatively strong, based on four randomised controlled trials, with clear benefits shown, although the duration of the trials was short. Its place in therapy was considered to be relatively low because its long-term safety is unknown and because established alternatives for adjunctive therapy are available.

**The Q rating relates to the drug’s position on the effectiveness indicator grid.** The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.

MTRAC reviewed zonisamide because it is a new drug with potential for prescribing in primary care.

**Licensed indication**

Zonisamide is indicated as adjunctive therapy in the treatment of adult patients (18 years or older) with partial seizures, with or without secondary generalisation.1

**Background information**

Epilepsy is one of the most common, serious brain disorders.2,3 It is characterised by recurrent, spontaneous epileptic seizures.

Epileptic syndromes fall into two main groups: generalised and partial seizures. Generalised seizures occur following simultaneous activation of both sides of the brain with loss of consciousness from the outset. If the discharge starts in a localised area of the brain, the seizure is termed partial or focal. A secondary generalised seizure may develop if the epileptic activity spreads to the entire brain. Complex partial seizures, with or without secondary generalisation, are the most common form of seizures in adult patients with refractory chronic epilepsy.

The prevalence of epilepsy is 0.4 to 1% of the population.3 In the majority of cases of epilepsy, no cause can be found, but seizures may occur in association with head trauma, CNS infections and brain tumours. Epilepsy is associated with an increased risk of premature death, and it may reduce life expectancy by up to 18 years.5

Patients often need to take their antiepileptic drugs for many years, potentially for life; therefore, consideration of adverse events is important. About 70% of patients diagnosed with epilepsy achieve complete seizure control with a single AED. The remaining 30% often require treatment with combinations of AEDs, and may continue to have seizures despite drug treatment.

Currently, sodium valproate, phenytoin and carbamazepine are used as monotherapy for the treatment of partial seizures with or without secondary generalisation. Several newer drugs are licensed for the same indication either as monotherapy or adjunctive therapy (lamotrigine, topiramate), or as adjunctive therapy only (gabapentin, levetiracetam, pregabalin, tiagabine, vigabatrin and zonisamide).

National Institute for Health and Clinical Excellence (NICE) guidance on the newer drugs (excluding zonisamide) was published in 2004.5 It recommended that these drugs should be used in patients refractory to treatment with the older AEDs or for whom older drugs are contraindicated. Combination therapy should be used only when monotherapy has failed.

**Clinical efficacy**

Four published double-blind RCTs compared the efficacy of zonisamide with placebo for the adjunctive treatment of patients with partial seizures.5-8 Only one of these studies used a treatment duration considered long enough by the European Medicines Agency (EMEA) for the assessment of efficacy of zonisamide for licensing for this indication.6
The minimum age was 17 years in two studies and 12 years in two studies. All patients had partial seizures not satisfactorily controlled by other AEDs. The studies included a baseline phase of 4 to 12 weeks, during which no study drug was given, followed by randomisation to receive zonisamide or placebo for periods of 12, 20 or 24 weeks (dose titration for four to seven weeks plus fixed-dose treatment for four to 18 weeks). The fixed doses of zonisamide used were 100, 300, or 500 mg daily, or up to 20 mg/kg/day. Other AEDs were continued throughout the studies.

The primary outcomes used were the median percentage change in frequency of seizures comparing the baseline period with the fixed-dose period (recorded by patients), and in two studies, the proportion of responders (patients with ≥ 50% decrease from baseline in seizure frequency) during the fixed-dose phase. Other outcomes included number of seizure-free days per 28-day period (reported for one study), and global assessment of improvement by physician and patient.

**Results**

There was a significantly greater reduction in the number of complex partial or all seizures with zonisamide treatment (400 mg or more daily, or up to 20 mg/kg/day) than with placebo treatment, from baseline to fixed-dose phase, in all studies.5-8 The median reductions in complex partial seizures ranged from 27 to 51% with zonisamide compared with changes of +4 to -16% with placebo (p < 0.05 for difference between groups). The differences were not significant with zonisamide 100 or 300 mg.6 The proportion of responders was significantly higher with zonisamide 400 or 500 mg per day than with placebo (p < 0.02).6,8 as well as in the two studies using up to 20 mg/kg/day. The numbers of responders ranged from 30 to 52% with zonisamide and from 9 to 22% with placebo.

The number of seizure-free days increased by three days with zonisamide, compared with 1.2 days with placebo (p value not reported).6 Global improvement (assessed by patients and physicians) occurred in greater numbers of patients taking zonisamide than placebo.

**Adverse effects**

Zonisamide patients experienced significantly more adverse events than patients taking placebo in all four studies.5-8 The most commonly reported adverse events associated with zonisamide were irritability, fatigue, dizziness, somnolence, headache, pharyngitis, anorexia and nausea. Ninety-two patients withdrew because of adverse events.

In one study, body weight was found to decrease in the zonisamide group by a mean value of 3.0 kg compared with a mean increase of 0.37 kg in the placebo group.5

For additional information on adverse events, refer to the Summary of Product Characteristics (SPC).

**Additional information**

- Zonisamide is contraindicated in patients who are allergic to sulphonamides.
- The recommended initial daily dose is 50 mg in two divided doses. After one week the dose may be doubled and then increased at one-week intervals in increments of up to 100 mg, to clinical effect or 500 mg daily, given once daily or divided. (In local practice, increments of 25 mg are used, and usually benefits are seen with lower doses than those used in the trials [personal communication].)
- When zonisamide treatment is to be discontinued, it should be withdrawn gradually.
- At current prices, the cost of one year’s treatment with zonisamide 200 mg daily is £817.

**References**