New drugs

Perampanel

Approved indication: epilepsy
Fycompa (Eisai)
2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg film-coated tablets
Australian Medicines Handbook section 16.1.3

Carbamazepine is considered to be the first-line treatment for partial-onset seizures. If it does not completely control the seizures there are several drugs which can be considered for adjunctive treatment. Perampanel adds to these options.

Glutamate is an excitatory neurotransmitter in the brain which may trigger seizures. Perampanel is a non-competitive antagonist at one of the glutamate receptors. By binding to the post-synaptic AMPA-glutamate receptor, perampanel is thought to reduce glutamate-induced neurotransmission.

Treatment begins with 2 mg at bedtime and is gradually increased according to the clinical response. Perampanel is completely absorbed. There is extensive metabolism which includes cytochrome P450 3A. This means that there is a potential for interactions with inducers and inhibitors of this enzyme system. As carbamazepine is an enzyme inducer it will lower plasma concentrations of perampanel and patients may need a higher dose of perampanel. The metabolites are excreted in the urine and faeces. The mean half-life of perampanel is 105 hours. Dose titration should only be done at a minimum of two-weekly intervals, unless the patient is taking a drug, such as carbamazepine, that shortens the half-life of perampanel. Lower doses may be

needed in patients with liver disease and perampanel is not recommended for patients with severe hepatic impairment or moderate and severe renal impairment.

The efficacy of perampanel was studied in three main trials involving patients with a minimum age of 12 years. They were experiencing partial seizures, with or without secondary generalised seizures, despite treatment with up to three antiepileptic drugs. After a baseline period of six weeks 1480 patients were randomised to add perampanel or a placebo. There was then a six-week titration phase followed by maintenance treatment for 13 weeks. The target doses of perampanel were 2 mg, 4 mg and 8 mg in one trial and 8 mg and 12 mg in the other two trials.

The median frequency of partial seizures at the start of the trials was 10–13 per 28 days. Pooled analysis of the three trials showed that perampanel reduced seizure frequency. The median percentage reduction in the frequency of partial seizures was 23.3% with 4 mg, 28.8% with 8 mg and 27.2% with 12 mg. These changes were significantly greater than the 12.8% reduction in the placebo group. There were also reductions in secondary generalised seizures, and a 50% reduction in seizure frequency was achieved by significantly more patients in the perampanel groups (see Table).

During the trials adverse events affected 77% of the perampanel groups and 66.5% of the placebo group. Symptoms which were more frequent with perampanel included dizziness, somnolence and fatigue. Adverse reactions resulted in the withdrawal of 4.8% of the patients taking placebo. In the perampanel groups the withdrawal rates were 3% with 4 mg, 8% with 8 mg and 19% with 12 mg. Some patients withdrew because

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Placebo</th>
<th>4 mg</th>
<th>8 mg</th>
<th>12 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly frequency of partial seizures at baseline</td>
<td>11.1</td>
<td>10</td>
<td>12.2</td>
<td>13</td>
</tr>
<tr>
<td>Median change in partial seizures after treatment</td>
<td>-12.8%</td>
<td>-23.3%</td>
<td>-28.8%</td>
<td>-27.2%</td>
</tr>
<tr>
<td>Monthly frequency of secondary generalised seizures at baseline</td>
<td>3.7</td>
<td>3.7</td>
<td>3.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Median change in secondary generalised seizures after treatment</td>
<td>-19.4%</td>
<td>-48.6%</td>
<td>-62.9%</td>
<td>-53.3%</td>
</tr>
<tr>
<td>Proportion of patients with &gt;50% reduction in partial seizures</td>
<td>19.3%</td>
<td>28.5%</td>
<td>35.3%</td>
<td>35%</td>
</tr>
<tr>
<td>Proportion of patients who became seizure-free after treatment</td>
<td>1%</td>
<td>4.3%</td>
<td>3.3%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>
of ataxia. Altered gait, balance disorder and falls were also reported. This could potentially be more of a problem in elderly patients, but the elderly were not well represented in the trials.

During the trials a weight gain of more than 7% body weight was more common in patients taking perampanel than those taking placebo (14.6% vs 7.1%).

Perampanel may provoke psychiatric problems. Some patients become angry and aggressive. Hostility and aggression were reported in 20% of the patients taking perampanel 12 mg daily versus 6% of the patients taking placebo. Like all antiepileptic drugs, perampanel may increase suicidal ideation.

As data are limited, perampanel is not recommended in pregnancy. It is unknown if the drug is excreted in breast milk. The efficacy of progestogen-containing oral contraceptives may be reduced by the 12 mg dose of perampanel.

Although adjunctive treatment with perampanel reduces the frequency of partial seizures, only a minority of patients will get a significant reduction and few will become seizure free. In the pooled analysis the proportion of patients having at least a 50% reduction in seizures was 28.5% with 4 mg, 35.3% with 8 mg and 35% with 12 mg (see Table). In one study this responder rate was not significantly different from placebo, but there were unexplained geographical differences in these results. The responder rates are better if the patient’s other treatment does not include enzyme inducing drugs. In the absence of head-to-head studies, a systematic review found perampanel’s efficacy, assessed by responder rates, was similar to lacosamide, retigabine and eslicarbazepine.

Manufacturer provided the product information

**REFERENCES**


* First published online 19 December 2014

The Transparency score (T) is explained in ‘New drugs: T-score for transparency’, Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov)

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu)

© At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)