MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support

Perampanel *(Fycompa®▼)*

For the adjunctive treatment of primary generalised tonic-clonic and focal seizures in epilepsy

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of perampanel:

- Current guidance from the National Institute for Health and Care Excellence (NICE) on the management of epilepsy (CG137, 2012) recommends that carbamazepine or lamotrigine, then levetiracetam, oxcarbazepine or sodium valproate are first- and second-line treatment options for focal seizures.
- For primary generalised tonic-clonic (PGTC) seizures, NICE recommends sodium valproate as a first-line treatment option, or lamotrigine if sodium valproate is unsuitable.
- It was the opinion of MTRAC that the clinical diagnosis, initial management and stabilisation of patients with refractory epilepsy are specialist functions. Once a person was stabilised on perampanel, it may be appropriate for primary care prescribers to continue maintenance treatment with the guidance of a shared care agreement or RICaD (Rationale for Initiation, Continuation, and Discontinuation).

Strength of the evidence for efficacy

The evidence for efficacy for perampanel as an adjunctive treatment was considered relatively weak. Three randomised controlled trials (RCTs) in people with partial-onset seizures, and one RCT in people with PGTC seizures showed that perampanel was associated with a greater response to treatment than placebo, but there are no trials that directly compared perampanel with other adjunctive treatments for epilepsy and evaluated seizure frequency.

MTRAC updated its guidance on perampanel due to the extension of the licensed indications

Description of technology

Perampanel is licensed for adjunctive treatment in:[1]

- patients with epilepsy aged 12 years and older, with partial-onset (or focal) seizures with or without secondarily generalised seizures,
- patients aged 12 years and older with idiopathic generalised epilepsy and PGTC seizures.

Perampanel is a first-in-class selective, non-competitive antagonist of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamate receptor on post-synaptic neurons.

Perampanel should be taken once daily, before bedtime. The recommended starting dose is 2 mg/day, titrated in 2 mg increments to a usual maintenance dose of 4 to 8 mg (max 12 mg/day), according to individual response. The interval between dose increases should be at least one week in people who are taking concomitant drugs that shorten the half-life of perampanel, and at least two weeks in other people. See the Summary of Product Characteristics (SPC) for a description of the interactions between perampanel and other anti-epileptic drugs.[1]

Background

Epilepsy is a term used to describe a group of disorders characterised by recurrent, spontaneous seizures, and caused by an abnormal excessive or synchronous neuronal activity in the brain.[2] Epileptic syndromes fall into two broad categories: generalised seizures (generalised tonic clonic, absence, myoclonic, tonic, and atonic seizures), which begin simultaneously in both cerebral hemispheres, and focal seizures (previously categorised as simple partial, complex partial, and secondary generalised tonic clonic seizures), that start in one or more localised areas in one hemisphere of the brain.[2;3] The prevalence of epilepsy is estimated to be about 9.7 cases per 1,000 people in the UK.[4] The condition is not necessarily life-long, and a person's epilepsy is considered resolved if they are seizure-free for 10 years and no longer receiving anti-epileptic drug (AED) treatment for five years.[2]

The NICE clinical guideline on the management of epilepsy recommendations on pharmacological treatment are that if monotherapy or adjunctive treatment with carbamazepine, lamotrigine, levetiracetam, oxcarbazepine or sodium valproate is ineffective or not tolerated for ***partial onset seizures***, advice should be sought from a tertiary care specialist. Additional AEDs that may be considered after referral are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.

For ***PGTC seizures***, sodium valproate is a first-line treatment option (or lamotrigine if sodium valproate is unsuitable). Carbamazepine and oxcarbazepine may also be considered, although there is a risk of exacerbating myoclonic or absence seizures. Clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate may be offered as adjunctive treatments. If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy (JME) is suspected, carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin are not recommended.

The Scottish Medicines Consortium (SMC) advised that perampanel should be restricted to second-line adjunctive treatment in patients with refractory partial onset epilepsy. Therapy should be initiated only by physicians who have appropriate experience in the treatment of epilepsy.[5] The SMC has not published guidance on perampanel for PGTC seizures.

Clinical evidence for efficacy and safety

Partial-onset seizures: Three phase 3, double-blind trials compared perampanel with placebo in a total of 1,480 participants aged at least 12 years with

uncontrolled partial-onset seizures despite prior therapy with at least two AEDs.[6-8] Eligible participants had at least five partial-onset seizures without a 25-day seizure-free period in the six-week pre-randomisation phases of the trials. During the trials, all participants took stable doses of one to three other AEDs. In two trials, participants were randomised to 8 or 12 mg perampanel once daily *vs.* placebo.[6;7] In the third trial, participants received perampanel doses of 2, 4 or 8 mg daily *vs.* placebo.[8] All three trials were of 19 weeks' duration; including a six-week dose titration period and a 13-week maintenance period. The primary outcome measures in all the trials were the percentages of participants with at least a 50% decrease in seizure frequency (European Medicines Agency [EMA] requirement), and the percentage change in seizure frequency per 28 days (US Federal Drug Agency requirement). Participants from the trials could enter an open-label extension study evaluating the long-term safety and tolerability of perampanel.[9]

Results: for both outcomes, perampanel at doses of 4 to 12 mg/day showed significantly lower seizure frequencies than placebo.

Participants showing ≥ 50% decrease in seizure frequency: significant differences were reported for doses of 4 to 12 mg daily.[8] For participants taking 4 mg/day perampanel, the placebo-subtracted responder rate was 10.6% (p = 0.013 *vs.* placebo, NNT = 9).[8] In participants taking 8[6-8] or 12[6;7] mg/day perampanel, the placebo-subtracted responder rates were 17 to 19%* (p < 0.001 *vs.* placebo, NNT = 5 or 6).

*[*Trial 304: only data from the subset of participants treated in North America are quoted due to systematic differences in the overall treatment of participants in North America compared with Central and South America.[6]]*

The median percentage reduction in seizure frequency per 28 days for placebo-treated participants was 9.7% or 10.7% in two trials[7;8] and 21% in the third trial.[6] Placebo subtracted mean reductions in seizure frequency were 12.6% (p = 0.003 *vs.* placebo) in the 4 mg/day perampanel group[8] and 5.3%[6] or 20 to 21%[7;8] (p < 0.05) in the 8 mg/day perampanel groups.[6-8] In the 12 mg/day group, placebo-subtracted median reductions in seizure frequency were 13.5% in one trial[6] (p = 0.016), and 7.9% in the second trial (p = 0.01).

PGTC seizures: One double-blind RCT evaluated perampanel for the adjunctive treatment of PGTC seizures in 164 participants with drug-resistant PGTC seizures and idiopathic generalised epilepsy[10]. Participants received perampanel (starting dose 2 mg/day) or placebo; the perampanel dose was up-titrated over four weeks to a target dose of 8mg/day or the highest tolerated dose (if lower). Participants then entered a 13-week maintenance phase.

The primary outcome was the percentage change in PGTC seizure frequency per 28 days (titration plus maintenance *vs*. baseline). The main secondary endpoint was the responder rate: percentage of participants achieving ≥ 50% reduction in PGTC seizure frequency during maintenance *vs*. baseline. This was also a primary outcome requirement for the EMA. Other outcomes included rate of freedom from PGTC and all seizures during the maintenance phase, and the Clinician's Global Impression of Change (CGI-C) (assessment of clinical status throughout the 4 weeks before Week 12, rated on a scale from 1 [very much improved] to 7 [very much worse]).

Results: Compared with placebo, there was a significantly greater improvement in PGTC seizure frequency with perampanel (decreases of 76.5% *vs.* 38.4%; p < 0.0001), and a treatment improved responder rate (64.2% *vs*. 39.5%; p < 0.0019).

Among secondary outcomes, more participants receiving perampanel were free of seizures than placebo (23.5% *vs*. 4.9%); statistical significance not reported. There was no significant difference between treatment groups for the CGI-C rating; 39.2% of perampanel-treated participants were rated 'much improved' or 'very much improved' *vs.* 32.9% of placebo-treated participants.

Adverse events

In the open-label, uncontrolled extension study,[9] (safety population: 1,216 from trials 304, 305 and 306) treatment-related adverse events were reported in 81.7% of participants, and adverse events led to discontinuation in 16%. The most common adverse events causing discontinuation were dizziness (48/1,216; 3.9%) and irritability (16/1,216; 1.3%); somnolence and headaches were also common adverse events. Serious psychiatric adverse events occurred in 47 participants, of which 12 (1%) related to aggression (n.b. 4 of the 12 participants had other psychiatric disorders in their medical history).[9]

Considerations for cost impact

- The cost of perampanel is £1,825 per patient per year.

References

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10. French JA et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy. A randomized trial. *Neurology* 2015; 85:1-8