Commissioning Support

Brivaracetam *(Briviact®▼)*

For the adjunctive treatment of focal seizures in epilepsy

Commissioning guidance:

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

- 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 brivaracetam, 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), according to local practice.
- 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. These guidelines pre-date the availability of brivaracetam.
- In the assessment report for brivaracetam, the European Medicines agency concluded that there was no effect on seizures observed for brivaracetam in participants receiving concomitant treatment with levetiracetam, which was likely due to the similar mode of action of levetiracetam and brivaracetam. Furthermore brivaracetam was less effective in patients with previous exposure to levetiracetam, compared with levetiracetam-naïve patients.

Strength of the evidence for efficacy

The evidence for efficacy for brivaracetam as an adjunctive therapy for epilepsy is relatively was considered relatively weak. Three randomised controlled trials (RCTs) in people with focal seizures showed that brivaracetam was associated with a significantly greater response to treatment than placebo, but there are no trials that directly compared brivaracetam with other adjunctive treatments for epilepsy and evaluated seizure frequency.

MTRAC considered brivaracetam because it was a new licensed product that primary care prescribers may be asked to prescribe.

Description of technology

Brivaracetam is a new antiepileptic drug licensed as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy.[1] *[Writer's note: The term partial onset seizures is used here as per the licensed indications; these are now more commonly referred to as focal seizures]*

Brivaracetam is available as an oral solution, a solution for injection or infusion and oral tablets. This review focusses on the evidence for the oral tablet formulation. The recommended starting dose of brivaracetam oral tablets is either 50 mg/day or 100 mg/day based on physician assessment of required seizure reduction *versus* potential side effects. The dose should be administered in two equally divided doses, once in the morning and once in the evening. Based on individual patient response and tolerability, the dose may be adjusted in the dose range of 50 mg/day to 200 mg/day.[1]

See the brivaracetam Summary of Product Characteristics (SPC) for full details.[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, 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 ***focal 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.[5]

The Scottish Medicines Consortium (SMC) advised that brivaracetam is accepted for restricted use within NHS Scotland. Use should be restricted to adjunctive therapy in patients with refractory partial onset epilepsy. Treatment should be initiated by physicians who have appropriate experience in the treatment of epilepsy.[6]

Clinical evidence for efficacy and safety

Three phase 3, double-blind, fixed-dose randomised controlled trials (RCTs; total n = 1,554; 1,097 receiving brivaracetam, 457 receiving placebo; duration 12 weeks) evaluated the efficacy of brivaracetam for seizure reduction.[7-9] They were of similar design and randomised adult and adolescent participants (≥ 16 years) with treatment-refractory focal epilepsy to adjunctive treatment with placebo or a fixed dose of

brivaracetam in addition to standard treatment of at least one AED. The doses of brivaracetam evaluated ranged from 5 to 200mg per day (only results for licensed 50mg, 100mg and 200mg doses reported here). Pooled data for these three trials were reported in one article (total n = 1,160)[11], and a further meta-analysis also included data from two additional phase 2 trials (total n = 2,399; 1,715 receiving brivaracetam and 684 receiving placebo).[10]

The primary outcome in two of the trials was the frequency of focal seizures per week.[7;9] In the third trial, the frequency of focal seizures per 28-day period was reported as a co-primary outcome with the percentage of participants showing at least a 50% reduction in focal seizure frequency per week.[8] This 'response rate' was reported as a secondary outcome in the other two trials.[7;9] The other common secondary outcome was the percentage of seizure-free participants during treatment.

Seizure frequency results from the individual trials for participants receiving brivaracetam 50mg per day were inconsistent (significantly lower frequency *vs*. placebo in one trial[7] but not in the other[8]). Two trials reported significantly greater reductions in focal seizure frequency *vs*. placebo for participants receiving brivaracetam 100mg daily[8;9], and one trial reported a significantly lower frequency of focal seizures per 28-days for brivaracetam 200mg daily *vs*. placebo.[8] The pooled-data analysis found significantly greater reductions in seizure frequency (per 28 days) for all licensed brivaracetam doses (50mg, 100mg and 200mg).[11]

Response rate (percentage of participants showing ≥ 50% reduction in seizure frequency): from the individual trials, the results for this outcome followed a similar pattern to the data for seizure frequency. Results for brivaracetam at 50mg per day were inconsistent[7;9], and a significantly greater response to treatment was noted for participants receiving brivaracetam at doses of 100[8;9] and 200mg[8] per day than with placebo treatment. The relative risk for this outcome across treatment groups in the meta-analysis was significantly in favour of brivaracetam treatment: 1.79 (95% CI 1.51 to 2.12).[10] Pooled analysis of data from the three phase 3 RCTs found a significantly greater response to treatment for all licensed brivaracetam doses (50mg, 100mg and 200mg).[11] In the larger meta-analysis *(that also included unlicensed 5mg and 20mg doses)*, a greater response to treatment was noted in participants who were not receiving concomitant treatment with levetiracetam *vs*. those who were.[10] The European Medicines Agency report also suggested that effectiveness may be lower in patients with prior exposure to levetiracetam *vs*. those with no exposure.[12]

Seizure freedom. During the 12-week trials, 2 to 5% of all brivaracetam-treated participants were seizure free; one trial only reported two seizure free participants with placebo treatment (0.8%)[8]. Data up to 24 months were reported in the SPC; 5.3 % of the subjects exposed to brivaracetam for 6 months (n = 1,500) were seizure free compared with 4.6 % and 3.7 % for subjects exposed for 12 months (n = 1,188) and 24 months (n = 847), respectively. However, discontinuation of participants due to lack of efficacy over that period may have introduced selection bias.[1] From the pooled analyses, brivaracetam treatment was significantly more likely to result in seizure freedom than placebo over the 12 week treatment period; RR 4.74 (95% CI 2.0 to 11.25).[10]

Adverse events

Adverse event data were reported in the three efficacy trials, and in a fourth RCT (n = 480; duration 16 weeks)[13] that evaluated the safety and tolerability of brivaracetam as primary outcome measures. Across the trials, treatment emergent adverse events (TEAEs) were reported in around 65 to 68% of brivaracetam-treated participants. The most frequently reported TEAEs were headache (9-14%), somnolence (11-16%), fatigue (7-11%) and dizziness (8 -14%). Psychiatric adverse events occurred in 1-5% of participants and included irritability, insomnia, depression and anxiety. The larger meta-analysis found a significantly greater risk of dizziness, somnolence, fatigue and irritability for brivaracetam *vs*. placebo.[10]

Considerations for cost impact

- There are an estimated 3,560 to 6,857 people in the West Midlands with focal seizures refractory to current treatment that may benefit from further treatment options *(based on NICE estimates of epilepsy incidence and 30% of patients refractory to AED treatment)*.
- At current prices, the cost of a years' treatment with brivaracetam is £1,690 (excluding VAT) for all dose formulations.

References

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