Brivaracetam in the management of epilepsy with focal seizures

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Brivaracetam (Briviact) is a new treatment for epilepsy, licensed as an adjunctive therapy in the management of partial-onset (focal) seizures with or without secondary generalisation. This article describes its indications, efficacy and adverse effects.

NEW PRODUCTS

ICE’s 2012 guideline on the management of epilepsy recommends monotherapy with carbamazepine or lamotrigine as first-line treatment for focal seizures; if this is unsuccessful, second-line choices are monotherapy with sodium valproate, levetiracetam or oxcarbazepine.\(^1\) If this still does not achieve seizure control, the options for adjunctive treatment are carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate.

Indications and dosage

Brivaracetam is a structural analogue of levetiracetam with a high and selective affinity for the target synaptic vesicle protein 2A, a transmembrane glycoprotein found in neurones and endocrine cells. It is licensed as adjunctive therapy in the treatment of partial-onset (focal) seizures with or without secondary generalisation in patients with epilepsy aged at least 16 years. It is available as tablets, an oral liquid and a solution for intravenous administration.

Treatment with brivaracetam should be initiated at a dosage of 25mg or 50mg twice daily and adjusted within the range 50–200mg daily. No dose adjustment is recommended for older people but clinical experience in patients older than 65 years is limited. No reduction in dosage is recommended for patients with impaired renal function but, if hepatic function is impaired, the starting dosage should be reduced to 25mg twice daily and the maximum dosage limited to 150mg daily. If treatment is discontinued, the dosage should be gradually reduced to 50mg daily, maintained at this level for one week then reduced to 20mg daily for one week.

Brivaracetam has a low risk of clinically significant interactions with other drugs (with the exception of rifampicin and St John’s wort, which may decrease plasma concentrations). Some other antiepileptic drugs (AEDs), such as carbamazepine, phenytoin and phenobarbital, may also decrease plasma concentrations of brivaracetam; however, no dose adjustment is recommended. No dose adjustment is required when co-administering with oral contraceptives.

Clinical trials

Three 12-week clinical trials provide the pivotal evidence for the efficacy of brivaracetam.\(^2,3\) Of these, two included some patients also taking levetiracetam.\(^2,3\) In the first, the dosage of brivaracetam was 5, 20 or 50mg daily\(^2\) and in the sec-

KEY POINTS

- Brivaracetam is a structural analogue of levetiracetam indicated as adjunctive treatment for epilepsy with focal seizures, with or without secondary generalised seizures
- It is associated with a low risk of clinically significant drug interactions
- The recommended dosage is 50–200mg daily in two equal doses
- In clinical trials, the 50 per cent responder rate to treatment with brivaracetam 100mg or 200mg daily was approximately 40 per cent
- Common adverse events include somnolence, dizziness and fatigue
- A month’s treatment costs £129.64 regardless of dosage
ond, the dosage was 20, 50 or 100mg daily. In a third trial, brivaracetam treatment was initiated at dosages of 100 or 200mg daily with no initial titration. The primary outcome in the first two trials was reduction in seizure frequency (the endpoint preferred by US regulators); the proportion of patients with at least a 50 per cent reduction in seizure frequency (50 per cent responder rate, preferred in Europe) was a co-primary endpoint in the third study and a secondary endpoint in the first two. These studies included patients who had experienced at least eight focal seizures during an eight-week pretreatment phase despite treatment with AEDs.

Pooled analysis of these trials, excluding patients treated with levetiracetam, included 903 patients assigned to treatment with brivaracetam and 418 to placebo. Mean age was 38 years. Just over half had never been treated with levetiracetam; 39 per cent had previously taken two to four AEDs and 36 per cent had taken five or more AEDs. The discontinuation rate was 3–4 per cent overall (vs 2 per cent with placebo).

The pooled analysis included outcomes for a dosage of 20mg daily, which are not reported here. The 50 per cent responder rates were significantly higher with brivaracetam at dosages of 50mg daily (34 per cent), 100mg daily (40 per cent) and 200mg daily (38 per cent) than with placebo (20 per cent) (see Table 1). This efficacy is similar to that reported for other AEDs approved recently.

There was no beneficial effect of concomitant treatment with brivaracetam and levetiracetam and prior treatment with levetiracetam was associated with slightly lower responder rates; the reasons for this are unclear. Baseline seizure frequency was eight to ten seizures per month. Compared with placebo, brivaracetam significantly reduced seizure frequency (by 20, 24 and 24 per cent with 50mg, 100mg and 200mg daily brivaracetam respectively). The proportion of patients who were seizure-free during treatment were 0.5 per cent with placebo and 3–5 per cent with brivaracetam.

Although these trials demonstrated little difference between dosages of 100mg daily and 200mg daily, most patients in longer-term studies were taking dosages above 100mg daily and patients previously treated with levetiracetam may respond better to higher doses.

Adverse effects
The overall frequency of treatment-emergent adverse events reported in clinical trials was 62 per cent with placebo and 68 per cent with brivaracetam; of these, 0.5 per cent were drug-related treatment-emergent severe adverse events. Common adverse events included somnolence (14 vs 9 per cent with placebo), dizziness (11 vs 7 per cent) and fatigue (8 vs 4 per cent). About 10 per cent of patients reported headache regardless of treatment assignment. Apart from injection site reactions, the nature and incidence of adverse events associated with intravenous administration of brivaracetam were similar to those reported with the oral formulation.

References

Declaration of interests
None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

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<td>Responder rate n/N (%)</td>
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Table 1. Pooled analysis from three trials: 50 per cent responder rate in partial-onset seizure frequency with brivaracetam versus placebo.