New Medicine Recommendation
Brivaracetam (Briviact®▼)

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.

Recommendation:

Red

- Medicine is supplied by the hospital for the duration of the treatment course.
- Primary care initiation or continuation of treatment is not recommended unless exceptional circumstances such as specialist GP.

Summary of supporting evidence:

- Brivaracetam is licensed for 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] [2] [3]
- It was accepted by the SMC for restricted use within NHS Scotland for 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. The SMC restricted the use for patients with refractory epilepsy and treatment should be initiated by physicians who have appropriate experience in the treatment of epilepsy. [4]
- There are no trials evaluating brivaracetam against an active comparator. It is difficult to ascertain the exact place in therapy for brivaracetam without this data. However, the SMC accepted lacosamide as the closest comparator based on data, supplied by the submitting company, from an indirect comparison model.

- The evidence for the efficacy of brivaracetam for the adjunctive therapy of partial-onset (focal-onset) seizures was presented in three (N01252, N01253 and N01358) phase III, randomised, double-blind, placebo-controlled, fixed-dose, multi-centre studies in patients aged 16 years and over. [2] [4]
- There was no significant difference for brivaracetam 50mg/day versus placebo for the primary endpoint for N01252. Although percentage reduction in focal seizure frequency in the 100mg/day sub-population was statistically significant (12% p = 0.037) this was classed as nominally significant by the investigators and the study was not considered positive.
- Data reported for N01253 and N01358 showed that results relating to the primary endpoints were statistically significant. [4]
- N01253 reported randomisation of 101 participants to receive brivaracetam 50mg/day and 96 to receive placebo. Median focal seizure reduction per week over placebo was 13% (p = 0.025). [4]
- N01358 reported randomisation of 252, 249 and 259 participants to 100mg/day, 200mg/day and placebo sub-groups respectively. The median reduction in focal seizure frequency per 28-day period over placebo for the 100mg/day sub-population was 23% (p < 0.001) and for the 200mg/day sub-population it was also 23% (p < 0.001). 50% responder rates were 39%, 38% (p < 0.001 for both) and 22% in the 100mg/day, 200mg/day and placebo sub-groups respectively. [4]
• Study N01125 reported that 853 patients were recruited and at 96 months of exposure of brivaracetam, 293 patients were still on treatment. The median reduction from baseline in seizure frequency per 28-day period was 42% in patients with partial-onset seizures on treatment. The proportion of patients with partial-onset seizures on treatment who were ≥50% responders was 43%. [4]
• In study N01199, 668 patients were recruited and after 90 months of exposure to brivaracetam, 239 patients were still on treatment. The median reduction from baseline in seizure frequency per 28-day period was 55% for patients on treatment. The proportion of patients on treatment who were ≥50% responders was 54%. [4]
• The most common treatment-emergent adverse events (occurring in ≥5% of patients in any group) were somnolence (14% [all doses of brivaracetam] versus 8.5% [placebo]), dizziness (11% versus 7.2%), headache (10.0% versus 10.2%) and fatigue (8.2% versus 3.7%). [4]
• The company submitting brivaracetam to the SMC chose lacosamide as the key comparator, which was accepted by the SMC. [4]
• Based on drug costs alone, the additional cost pressure per cohort of 20 patients across Lancashire per year if brivaracetam is used in preference to lacosamide = £186 x 20 = £3,720 (range [lowest and maximum dose comparison]: +£11,200 to -£3,780 [cost saving realised at maximum dose]).
• The SMC conducted an economic analysis which concluded that when additional costs were taken into account, over a two year time horizon, brivaracetam cost £2 per patient less than lacosamide (£40 cost saving across the Lancashire NHS footprint over two years). This analysis did not include costs associated with titration regimens. [4]
### Details of Review

<table>
<thead>
<tr>
<th><strong>Name of medicine</strong> (generic &amp; brand name):</th>
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<tbody>
<tr>
<td>Brivaracetam (Briviact)</td>
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<table>
<thead>
<tr>
<th><strong>Strength(s) and form(s):</strong></th>
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<tbody>
<tr>
<td>Film-coated tablets – various strengths. Oral solution 10mg/ml. Solution for injection or infusion 10mg/ml.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th><strong>Dose and administration:</strong></th>
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<tbody>
<tr>
<td>The recommended starting dose 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.</td>
</tr>
</tbody>
</table>

Brivaracetam may be initiated with either intravenous or oral administration. When converting from oral to intravenous administration or vice versa, the total daily dose and frequency of administration should be maintained. Brivaracetam solution for injection/infusion is an alternative for patients when oral administration is temporarily not feasible. There is no experience with twice daily intravenous administration of brivaracetam for a period longer than four days.

Film-coated tablets must be taken orally swallowed in whole with liquid and may be taken with or without food.

<table>
<thead>
<tr>
<th><strong>BNF therapeutic class / mode of action</strong></th>
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<tbody>
<tr>
<td>Not listed in BNF (checked 13/07/16). Binds to synaptic vesicle protein 2A (SV2A) in the brain.</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Licensed indication(s):</strong></th>
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<tbody>
<tr>
<td>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] [2] [3]</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Proposed use</strong> (if different from, or in addition to, licensed indication above):</th>
</tr>
</thead>
<tbody>
<tr>
<td>As per licensed indication.</td>
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<table>
<thead>
<tr>
<th><strong>Course and cost:</strong> [3] [2] [1]</th>
</tr>
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<tbody>
<tr>
<td>10mg white tab, 14=£34.64.</td>
</tr>
<tr>
<td>25mg grey tab, 56=£129.64.</td>
</tr>
<tr>
<td>50mg yellow tab, 56=£129.64.</td>
</tr>
<tr>
<td>75mg purple tab, 56=£129.64.</td>
</tr>
<tr>
<td>100mg green tab, 56=£129.64.</td>
</tr>
<tr>
<td>10mg/ml oral solution, 300ml=£115.83.</td>
</tr>
<tr>
<td>10mg/ml solution for injection/infusion, 10 x 5ml=£222.75.</td>
</tr>
</tbody>
</table>

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*In the NICE recommendation, 'partial seizures' has been replaced with 'focal seizures' to reflect a change in terminology since the original guideline was published in 2004.*
Current standard of care/comparator therapies:
The applicant states that brivaracetam would be used third line (or later) – as an alternative to perampanel, zonisamide or lacosamide. Lacosamide is used as comparator in the SMC review – for rationale, see section: ‘Summary of evidence on cost effectiveness’.

Relevant NICE guidance:

NICE CG 137 [5]

1.9.3 Pharmacological treatment of focal seizures

First-line treatment in children, young people and adults with newly diagnosed focal seizures

1.9.3.1 Offer carbamazepine or lamotrigine as first-line treatment to children, young people and adults with newly diagnosed focal seizures.

1.9.3.2 Levetiracetam is not cost effective at June 2011 unit costs^b. Offer levetiracetam, oxcarbazepine or sodium valproate (provided the acquisition cost of levetiracetam falls to at least 50% of June 2011 value documented in the National Health Service Drug Tariff for England and Wales) if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these five AEDs (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine or sodium valproate). Be aware of the teratogenic and developmental risks of sodium valproate.

1.9.3.3 Consider adjunctive treatment if a second well-tolerated AED is ineffective.

Adjunctive treatment in children, young people and adults with refractory focal seizures

1.9.3.4 Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with focal seizures if first-line treatments are ineffective or not tolerated. Be aware of the teratogenic and developmental risks of sodium valproate.

1.9.3.5 If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields.

^b Estimated cost of a 1500 mg daily dose was £2.74 at June 2011. In July 2016 the cost of a daily 1500mg dose was 33p Cost taken from the Drug Tariff online accessed 18 July 2016 http://www.drugtariff.nhsbsa.nhs.uk/#/00330394-DD/DD00330118/Part VIIIIA products L
Background and context

Epilepsy is a disorder of the brain characterised by the recurrence of spontaneous, unprovoked seizures. [6]

Epilepsy includes many clinical situations which differ by age on onset, type of seizures, aetiological background, resulting disability, prognosis and response to treatment. The main groups of epilepsy are focal (partial) onset seizures, related to a focal brain dysfunction (approximately 60% of epilepsy cases), and generalised seizures which represent approximately 30% of cases. In the remaining 10% the classification is uncertain. [6]

The lifetime risk of developing epilepsy (defined as a history of epilepsy regardless of the frequency of seizures or use of antiepileptic medication) is between 3% and 5%, with the highest incidence reported in neonates, young children and the elderly. The prevalence of active epilepsy is estimated at 5 – 8 per 1000 people in high-income countries and 10 per 1000 in low-income countries. [6]

The primary treatment option for epilepsy is antiepileptic drugs (AEDs) aiming at preventing or reducing seizures as quickly as possible. Improved seizure control is likely to reduce morbidity and premature mortality associated with continuing seizures, especially convulsive attack. It is estimated that between 70% – 80% of adults with new onset epilepsy will become seizure free with available AEDs, although half will experience adverse effects [6]

Drug resistant epilepsy occurs in 20%-30% of patients newly diagnosed with epilepsy depending on the definition used.

Pharmacology and pharmacokinetics

Brivaracetam has a high selectivity for synaptic vesicle protein 2A (SV2A), a transmembrane glycoprotein found at presynaptic level in neurons and in endocrine cells. Although the exact role of this protein remains to be elucidated it has been shown to modulate exocytosis of neurotransmitters. Binding to SV2A is believed to be the primary mechanism for brivaracetam anticonvulsant activity. [2]

Brivaracetam follows linear kinetics at doses below 600mg (the maximum licensed dose is 200mg). [2]

Brivaracetam is rapidly and completely absorbed after oral administration and the absolute bioavailability is approximately 100%. Administration of brivaracetam alongside a high-fat meal can reduce the C_max by as much as 37% although the extent of absorption is unchanged. [2]

Brivaracetam has a volume of distribution of around 0.5L/kg; brivaracetam is weakly bound to plasma proteins.

Brivaracetam is primarily metabolised by hydrolysis and hydroxylation. The three main metabolic products of brivaracetam are not pharmacologically active. [2]

Brivaracetam is primarily eliminated by metabolism and excretion in the urine. More than 95% of a dose is excreted in the urine within 72 hours of intake. Less than 10% of a dose is excreted in the urine unchanged. The terminal plasma half-life is approximately nine hours. [2]

Summary of evidence

Summary of efficacy data in proposed use:

The review conducted by the SMC in July 2016 was used as the main foundation for this review. [4]

The most significant evidence for the efficacy of brivaracetam for the adjunctive therapy of partial-onset (focal-onset) seizures is from three phase III, randomised, double-blind, placebo-controlled,
fixed-dose, multi-centre studies in patients aged 16 years and over. [2] [4]

The three studies were designated: N01252, N01253 and N01358. Patients in all three studies had well-characterised focal epilepsy or epileptic syndromes according to the International League Against Epilepsy (ILAE) criteria, with a history of partial-onset seizures with or without secondary generalisation. At screening, patients had been receiving one or two concomitant AEDs at a stable and optimal dosage for at least a month prior to enrolling in the trial and were continued throughout the study. [4]

Following the baseline period, eligible patients were randomised equally to 12-weeks treatment with placebo or brivaracetam. Each study assessed a different combination of dose regimens:

**Table 1 - Dose regimens assessed in brivaracetam efficacy studies**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Brivaracetam Dose Regimens Assessed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N01252</td>
<td>20mg/day**, 50mg/day or 100mg/day</td>
</tr>
<tr>
<td>N01253</td>
<td>5mg/day**, 20mg/day or 50mg/day</td>
</tr>
<tr>
<td>N01358</td>
<td>100mg/day or 200mg/day</td>
</tr>
</tbody>
</table>

*Each daily dose was given in two equally divided doses.

**Results from this sub-population were not reported by the SMC – see below.

The dose regimens studied were kept as fixed doses, with no dose titration. Only one dose reduction was permitted. Patients were stratified by concomitant use of levetiracetam in studies N01252 and N01253 (limited to 20% of the study population) and geographical region. Following completion of the 12-week study period, patients entered a long-term follow-up study or underwent a down-titration. [4]

**Table 2 - Assessment of study interventions and comparators**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>N01252</td>
<td>Brivaracetam 20mg/day, 50mg/day or 100mg/day</td>
<td>Placebo</td>
<td>Percent reduction over placebo in the focal seizure frequency per week over the treatment period</td>
</tr>
<tr>
<td>N01253</td>
<td>Brivaracetam 5mg/day, 20mg/day or 50mg/day</td>
<td>Placebo</td>
<td>Percent reduction over placebo in the focal seizure frequency per week over the treatment period</td>
</tr>
<tr>
<td>N01358</td>
<td>Brivaracetam 100mg/day or 200mg/day</td>
<td>Placebo</td>
<td>Percentage reduction over placebo in the focal seizure frequency per 28 days over the treatment period and ≥50% responder rate (proportion of patients with ≥50% reduction in seizure frequency).</td>
</tr>
</tbody>
</table>

Analyses were conducted on the intention-to-treat (ITT) population in studies N01252 and N01358 and in the modified ITT population in N01253. [4]

The SMC only reported results from the three studies that related to licensed doses (50 – 200mg total daily dose). The results that were reported for each sub-population that received a licensed dose of brivaracetam were as follows:

**Table 3 - results of primary and secondary endpoints for licensed doses of brivaracetam in studies N01252 and N01253 [4]**
Table 4 - results of co-primary and secondary endpoint for licensed doses of brivaracetam in study N01358. [4]

<table>
<thead>
<tr>
<th>Study N01252</th>
<th>Study N01358</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td><strong>Primary endpoint</strong></td>
</tr>
<tr>
<td>Median POS frequency/week at baseline</td>
<td>Median POS frequency/week at baseline</td>
</tr>
<tr>
<td>Brivaracetam 50mg/day (n=99)</td>
<td>Brivaracetam 100mg/day (n=100)</td>
</tr>
<tr>
<td>Brivaracetam 100mg/day (n=101)</td>
<td>Placebo (n=96)</td>
</tr>
<tr>
<td>Median reduction in focal seizure frequency/week over placebo, %</td>
<td>Median reduction in focal seizure frequency/week over placebo, %</td>
</tr>
<tr>
<td>1.80</td>
<td>2.0</td>
</tr>
<tr>
<td>6.5%</td>
<td>12%</td>
</tr>
<tr>
<td>p=0.261</td>
<td>p=0.037 (nominal)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Secondary endpoints</strong></th>
<th><strong>Secondary endpoints</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% responder rate, % (n/N)</td>
<td>≥50% responder rate, % (n/N)</td>
</tr>
<tr>
<td>27% (27/99)</td>
<td>38% (98/100)</td>
</tr>
<tr>
<td>Proportion of patients seizure free, % (n/N)</td>
<td>Proportion of patients seizure free, % (n/N)</td>
</tr>
<tr>
<td>0%</td>
<td>4.0% (4/100)</td>
</tr>
<tr>
<td>p=0.339</td>
<td>p=0.023</td>
</tr>
</tbody>
</table>

There was no significant difference for brivaracetam 50mg/day versus placebo in the primary endpoint for N01252. Although percentage reduction in focal seizure frequency in the 100mg/day sub-population was statistically significant (12% p = 0.037) this was classed as nominally significant by the investigators and the study was not considered positive. Data reported for N01253 and N01358 showed that results relating to the primary endpoints were statistically significant. [4]

N01253 reported randomisation of 101 participants to receive brivaracetam 50mg/day and 96 to receive placebo. Median focal seizure reduction per week over placebo was 13% (p = 0.025). [4]

N01358 reported randomisation of 252, 249 and 259 participants to 100mg/day, 200mg/day and placebo sub-groups respectively. The median reduction in focal seizure frequency per 28 day period over placebo for the 100mg/day sub-population was 23% (p < 0.001) and for the 200mg/day sub-population it was also 23% (p < 0.001). 50% responder rates were 39%, 38% (p < 0.001 for both) and 22% in the 100mg/day, 200mg/day and placebo sub-groups respectively. [4]

A pooled analysis was conducted that included participants in all three studies excluding those that were receiving levetiracetam (around 19% of participants in studies N01252 and N01253). There were statistically significant reductions over placebo in focal-onset seizure frequency per 28 day period for brivaracetam 50mg/day (20%), 100mg/day (24%) and 200mg/day (24%). The ≥50% responder rates were 34%, 39% and 38% for 50mg/day, 100mg/day and 200mg/day.
respectively and 20% for placebo (all p-values were ≤ 0.001 versus placebo). The proportion of patients that were seizure free during the entire treatment period were 2.5% for 50mg/day, 5.1% 100mg/day, 4.0% for 200mg/day and 0.5% for placebo. [4]

Other efficacy data:

Two open-label, long-term studies were on-going at the point the SMC review was published. Patients were treated with brivaracetam at a starting dose from the previous study and the patient was titrated up to 200mg/day. Interim analysis of the studies was available to the SMC. [4]

Study N01125 reported that 853 patients were recruited and at the clinical cut-off, when there was up to 96 months of exposure of brivaracetam, 293 patients were still on treatment. The median reduction from baseline in seizure frequency per 28day period was 42% in patients with partial-onset seizures on treatment. The proportion of patients with partial-onset seizures on treatment who were ≥50% responders was 43%. [4]

In study N01199, 668 patients were recruited and at the clinical cut-off (after 90months of exposure to brivaracetam), 239 patients were still on treatment. The median reduction from baseline in seizure frequency per 28day period was 55% for patients on treatment. The proportion of patients on treatment who were ≥50% responders was 54%. [4]

Summary of safety data:

There are no safety data versus an active comparator. The European Medicines Agency (EMA) noted that the safety profile of brivaracetam was acceptable and as expected based on experience with levetiracetam. [4]

Pooled safety data from the pivotal studies described previously have been reported. Investigator determined drug related adverse events occurred in 47%, 40%, 44% and 30% of patients in the brivaracetam 50mg/day, brivaracetam 100mg/day, brivaracetam 200mg/day and placebo groups respectively. Investigator determined drug-related serious adverse events occurred in 0.5%, 0.8%, 0.8% and 0.4% of patients in the brivaracetam 50mg/day, brivaracetam 100mg/day, brivaracetam 200mg/day and placebo groups respectively. [4]

The most common treatment-emergent adverse events (occurring in ≥ 5% of patients in any group) were somnolence (14% [all doses of brivaracetam] versus 8.5% [placebo]), dizziness (11% versus 7.2%), headache (10.0% versus 10.2%) and fatigue (8.2% versus 3.7%). [4] All significant adverse reactions observed during clinical trials were:

Table 5 - summary of adverse effects by organ class. The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. [2]
Psychosis is considered to be more prevalent in patients with epilepsy and AEDs can induce psychotic disorders. Given the reports of psychosis from the brivaracetam clinical studies, and that a causal relationship with brivaracetam could not be excluded, psychotic disorder has been included in the undesirable effects section of the summary of product characteristics (SPC).

Patients treated with brivaracetam have reported suicidal ideation or behaviour, and suicidal ideation has also been included as an AED class warning uncommon adverse drug reaction in the SPC. [4]

Brivaracetam has minor or moderate influence on the ability to drive and use machines.

**Interaction with other medicinal products**

**Pharmacodynamic interactions**

There is no observed benefit if brivaracetam and levetiracetam are administered concurrently, additionally there are no known safety or tolerability concerns. [2]

Brivaracetam approximately doubles the psychomotor function, attention and memory effects of ethanol. Intake of brivaracetam with ethanol is not recommended. [2]

**Pharmacokinetic interactions – effects of other medicinal products on brivaracetam**

Brivaracetam plasma concentration may be increased by the following: [2]

- CYP2C19 inhibitors e.g. fluvoxamine, fluconazole.

Brivaracetam plasma concentration may be reduced by the following: [2]

- Rifampicin – prescribers should consider adjusting the dose of brivaracetam
- St John’s wort
- Carbamazepine – no dose adjustment required
- Phenobarbital – no dose adjustment required
- Phenytoin – no dose adjustment required

**Pharmacokinetic interactions – effects of other brivaracetam on other medicinal products**

Brivaracetam may increase the plasma concentration of medicinal products metabolised by CYP2C19 e.g. lansoprazole, omeprazole and diazepam. Brivaracetam has been show to induce CYP3A4 and CYP2B6 in vitro, although only induction of CYP2B6 has been replicated in vivo. Therefore, caution should be exercised by prescribers when using drugs metabolised via this
pathway e.g. efavirenz. [2]

Brivaracetam significantly increases the plasma concentration of the active carbamazepine metabolite carbamazepine-epoxide. [2]

Brivaracetam also increased the \( C_{\text{max}} \) and AUC of phenytoin by 20%. The SPC advises that no dose adjustment is required. [2]

Co-administration of brivaracetam (100 mg/day) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) did not influence the pharmacokinetics of either substance. When brivaracetam was coadministered at a dose of 400 mg/day (twice the recommended maximum daily dose) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg), a reduction in estrogen and progestin AUCs of 27% and 23%, respectively, was observed without impact on suppression of ovulation. There was generally no change in the concentration-time profiles of the endogenous markers estradiol, progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and sex hormone binding globulin (SHBG). [2]

**Pregnancy and Lactation**

As a precautionary measure, brivaracetam should not be used during pregnancy unless clinically necessary. There is a limited amount of data from the use of brivaracetam in pregnant women. If a woman decides to become pregnant, the use of brivaracetam should be carefully re-evaluated. [2]

There is no data on placental transfer in humans, but brivaracetam was shown to readily cross the placenta in rats. The potential risk for humans is unknown. [2]

It is not known if brivaracetam is excreted in human breast milk. [2]

**Strengths and limitations of the evidence:**

**Limitations**

1. Brivaracetam was not significantly superior to placebo for \( \geq 50\% \) responder rates in study N01252 (\( \geq 50\% \) responder rates was the preferred primary endpoint for the EMA). [4]
2. No significant difference between brivaracetam and placebo in study N01252. [4]
3. Sub-group analyses of studies N01252 and N01253 showed no benefit for brivaracetam in patients taking concomitant levetiracetam. [4]
4. Studies were initiated before the ILAE definition of drug-resistant epilepsy was agreed. Therefore, patients recruited to the studies were not required to have failed on two adequate trials of AED regimens (the EMA considered the study populations to be drug-resistant based on their high baseline seizure frequency and inadequate seizure control with at least one AED trial). [4]
5. Limited conclusions can be drawn from the long-term, open-label studies:
   a. Selection bias as those entering the studies may have responded better to the drug during the double-blind studies compared to those that discontinued from them.
   b. High attrition rates due to lack of efficacy.

**Strengths**

1. Significant difference between brivaracetam and placebo in studies N01253 and N01358. [4]
2. All studies reviewed as part of the regulatory process were of good quality. [4]

**Summary of evidence on cost effectiveness:**
**Background**

The company submitting brivaracetam to the SMC chose lacosamide as the key comparator, which was accepted by the SMC. This is relevant to the LMMG review as the applicant states that brivaracetam would be used third line (or later) as an alternative to perampanel, zonisamide or lacosamide. Lacosamide is restricted for use in refractory epilepsy. The company chose lacosamide as comparator for the SMC review because it has the highest market share of the AEDs only licensed for adjunctive treatment. The validity of the approach was questioned by the SMC, given the range of AEDs described by clinical experts. [4]

Comparative efficacy data was supplied to support the economic analysis (cost-minimisation analysis). Three studies for both brivaracetam and lacosamide were compared. The efficacy outcomes reported were: percentage reduction in partial-onset seizure frequency, 50% responder rate and proportion of patients that were seizure free. Two safety outcomes were also reported. Following baseline adjustments, there was no significant difference between treatments for the efficacy and safety outcomes analysed. [4]

The SMC stated that submitting company also noted that a network meta-analysis had been undertaken comparing brivaracetam with: eslicarbazine, lacosamide, perampanel and retigabine for adjunctive treatment of partial-onset seizures. The results showed no significant differences between any adjunctive anti-epileptic drugs for partial-onset seizures. The SMC did state that the search strategy had not been appraised which was a limitation. [4]

**Comparative health economic evidence**

**Cost-minimisation analysis:**

The analysis compares brivaracetam as adjunctive therapy with lacosamide for the treatment of partial-onset seizures with or without secondary generalisation in adults and adolescent patients from 16 years with epilepsy. The evidence to support the cost-minimisation analysis is presented above (see ‘Background’). The results are presented over a two-year time horizon. [4]

The SMC observed that the costs in the model related only to medicine acquisition costs for both treatments for the maintenance phase of treatment only. Lacosamide was associated with lower medicine acquisition costs in the titration phase. However, the submitting company successfully argued that differences in cost would be negligible when the cost of monitoring therapy was considered. Therefore, the cost-minimisation analysis focused on the maintenance costs only. [4]

The SMC stated that brivaracetam costs £3,080 over the two-year time horizon compared to £3,082 for lacosamide. A difference of £2 in favour of brivaracetam. [4] The current costs of brivaracetam and lacosamide remain unchanged, therefore the SMC’s analysis would remain unchanged.

The SMC concluded that the economic case had been demonstrated. [4]

**Prescribing and risk management issues:**

Brivaracetam is a prescription only medicine and supply is subject to a prescription. Brivaracetam is licensed for use as an adjunct to other AEDs and, as such, it should be initiated by a specialist experienced in the management of epilepsy and related disorders. There are no special precautions required for the storage of brivaracetam.

**Commissioning considerations:**

**Comparative unit costs:** [4]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Example regimen</th>
<th>Pack cost</th>
<th>Cost per patient per course/ per year (ex VAT)</th>
</tr>
</thead>
</table>

October 2016

NOT FOR COMMERCIAL USE

NHS Midlands and Lancashire CSU
## Brivaracetam

<table>
<thead>
<tr>
<th>Dose</th>
<th>Description</th>
<th>Price</th>
</tr>
</thead>
</table>
| 25mg – 100mg p.o. b.d. | 10mg tablets x 14 = £34.64.  
25mg, 50mg, 75mg and 100mg tablets x 56 = £129.64.  
10mg/ml oral solution x 300ml = £115.83.  
10mg/ml injection x 5ml x 10 = £222.75. | £1,685  |

## Lacosamide

<table>
<thead>
<tr>
<th>Dose</th>
<th>Description</th>
<th>Price</th>
</tr>
</thead>
</table>
| 100mg – 200mg p.o. b.d. | 50mg tablets x 14 = £10.81.  
100mg tablets x 14 = £21.62, x 56 = £86.50.  
150mg tablets x 14 = £32.44, x 56 = £129.47.  
200mg tablets x 56 = £144.16.  
10mg/ml syrup x 200ml = £25.74.  
10mg/ml infusion x 20ml = £29.70. | £1125 – £1874 |

This table does not imply therapeutic equivalence of drugs or doses. Prices eMIMS: July 2016

### Associated additional costs or available discounts:

It is not expected that additional outpatient clinic appointments will be required. There are no known currently available manufacturer discounts.

### Productivity, service delivery, implementation:

There is limited potential for increased demand in primary and secondary care services. Brivaracetam is another treatment option for drug-resistant or refractory epilepsy and patients would be reviewed according to their existing appointment schedule.

### Anticipated patient numbers and net budget impact:

The applicants stated that they expected twenty patients per year across the Lancashire footprint to be treated with brivaracetam in their organisation.

The applicant states that the main comparator therapies are: perampanel, lacosamide and zonisamide. The SMC accepted, after representation by the submitting company, that lacosamide was the main comparator. [4]

**Annual cost of treatment across the Lancashire health economy (drug cost only):**

**Brivaracetam:**

- Estimated number of patients annually across Lancashire = 20
- Projected cost of treatment at the lowest licensed dose across Lancashire per year = 20 x £1,685 = £33,700
- Cost of treatment at the maximum dose per year = 60 x £1,685 = £33,700

**Lacosamide:**

- Estimated number of patients annually across Lancashire = 20 (comparator)
- Projected cost of treatment at the lowest licensed dose across Lancashire per year = 20 x £1,125 = £22,500
- Cost of treatment at the maximum dose per year = 20 x £1,874 = £37,480

**Average cost of treatment per patient per year =**
Brivaracetam = (£33,700 + £33,700)/40 = £1,685
Lacosamide = (£22,500 + £37,480)/40 = £1,499

**Difference in cost between brivaracetam and lacosamide per patient per year using the average dose** =
£1,685 – £1,499 = £186

**Difference in cost at the maximum dose** =
£1,685 – £1,874 = -£189

**Difference in cost at the lowest licensed dose** =
£1,685 – £1,125 = £560

Based on drug costs alone, the additional cost pressure per cohort of 20 patients across Lancashire per year if brivaracetam is used in preference to lacosamide = £186 x 20 = £3,720 (range [lowest and maximum dose comparison]: +£11,200 to -£3,780 [cost saving realised at maximum dose]).

The SMC conducted an economic analysis (discussed above) which concluded that when additional costs were taken into account, over a two year time horizon, brivaracetam cost £2 per patient less than lacosamide (£40 cost saving across the Lancashire NHS footprint over two years).

**Innovation, need, equity:**

Brivaracetam is not an innovative new treatment. Brivaracetam is a structural analogue of levetiracetam and has a similar mechanism of action.

The applicant has stated brivaracetam will offer an additional therapy alternative therapy to drug resistant patients.

The SMC has approved brivaracetam for restricted use. There is a commissioning picture in England of either ‘RAG’ rating brivaracetam red or black.

Around 20% to 30% of newly diagnosed patients will have drug resistant epilepsy. The International League against Epilepsy (ILAE) defines drug-resistant epilepsy as failure of adequate trials of two tolerated and appropriately chosen AED schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom. [6]

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area in patients with treatment resistant/refractory epilepsy. [4]

**References**


[4] Scottish Medicines Consortium, “Bivaracetam 10mg, 25mg, 75mg, 100mg film-coated tablets; 10mg/mL oral solution; 10mg/mL solution for injection/infusion (Briviact) SMC No. (1160/16),” Scottish Medicines Consortium - assessment and advice, 11 July 2016.

