New Medicine Recommendation

Brivaracetam (Briviact®▼)

Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy

Recommendation:

Amber0

- Suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Little or no specific monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Brief prescribing document or information sheet may be required.

Summary of supporting evidence:

- Briviact is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 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 4 years to ≤15 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. The SMC has previously accepted brivaracetam for restricted use 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. [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.
- It was accepted by AWMSG for restricted use within NHS Wales. Brivaracetam (Briviact®) should be restricted for use in the treatment of patients with refractory epilepsy, who remain uncontrolled with, or are intolerant to, other adjunctive anti-epileptic medicines, within its licensed indication as adjunctive therapy in the treatment of partial-onset seizures (POS) with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy. Brivaracetam (Briviact®) is not recommended for use within NHS Wales outside of this subpopulation.[5]
- 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 101participants 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 28day 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 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 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]
- 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]
- In children aged 4 years and older, partial onset seizures have a similar clinical expression to those in adolescents and adults. Experience with epilepsy medicines suggests that the results of efficacy studies performed in adults can be extrapolated to children down to the age of 4 years provided the paediatric dose adaptations are established and safety has been demonstrated. Doses in patients from 4 years of age were defined by weight-based dose adaptations which have been established to achieve similar plasma concentrations to the ones observed in adults taking efficacious doses.[1][2][3]
- A long-term, uncontrolled, open-label safety study included children (from 4 years to less than 16 years) who continued treatment after completing the PK study and children directly enrolled into the safety study. Children who directly enrolled received a brivaracetam starting dose of 1 mg/kg/day and depending on response and tolerability, the dose was increased up to 5 mg/kg/day by doubling the dose at weekly intervals. No child received a dose greater than 200 mg/day. For children weighing 50 kg or greater the brivaracetam starting dose was 50 mg/day and depending on response and tolerability, the dose was increased up to a maximum of 200 mg/day by weekly increments of 50 mg/day. From the pooled open-label safety and PK studies in adjunctive therapy, 149 children have received brivaracetam, of whom 116 have been treated for ≥6 months, 107 for ≥12 months, 58 for ≥24 months, and 28 for ≥36 months.The efficacy and tolerability of brivaracetam in paediatric patients less than 4 years of age have not been established. Brivaracetam was evaluated in these patients in a short term openlabel pharmacokinetic study and an ongoing open-label extension study, in 16 subjects from 1 month to <4 years of age.[1]1[2][3]
- In a pharmacokinetic study with a 3-week evaluation period and weekly fixed 3-step up-titration using the brivaracetam oral solution, 99 subjects aged 1 month to <16 years were evaluated. Brivaracetam was administered at weekly increasing doses of approximately 1 mg/kg/day, 2 mg/kg/day, and 4 mg/kg/day. All doses were adjusted by body weight, and did not exceed a maximum of 50 mg/day, 100 mg/day, and 200 mg/day. At the end of the

evaluation period, subjects may have been eligible for entry into a long-term follow-up study continuing on their last received dose. Plasma concentrations were shown to be dose-proportional in all age groups. Population pharmacokinetics modeling indicated that the dose of 2.0 mg/kg twice a day provides the same steady-state average plasma concentration as in adults receiving 100 mg twice daily. The estimated plasma clearance was 1.61 L/h, 2.18 L/h and 3.19 L/h for children weighing 20 kg, 30 kg and 50 kg, respectively. In comparison, plasma clearance was estimated at 3.58 L/h in adult patients (70 kg body weight). Currently, no clinical data are available in neonates.[1][2][3]

- The safety profile of brivaracetam observed in children was consistent with the safety profile observed in adults. In the open label, uncontrolled, long-term studies suicidal ideation was reported in 4.7 % of paediatric patients (more common in adolescents) compared with 2.4 % of adults and behavioural disorders were reported in 24.8 % of paediatric patients compared with 15.1 % of adults. The majority of events were mild or moderate in intensity, were non-serious, and did not lead to discontinuation of study drug. An additional adverse reaction reported in children was psychomotor hyperactivity (4.7 %).[1][2][3]
- There are limited safety data from open-label studies in children from 1 month to <4 years of age. Limited data are available on neurodevelopment in children <4 years of age. No clinical data are available in neonates.[1][2][3]
- The SMC conducted an economic analysis which concluded that when additional costs were taken in to 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

Name of medicine (generic & brand name)**:**

Brivaracetam (Briviact) [1][2][3]

Strength(s) and form(s):

Film-coated tablets – various strengths. Oral solution 10mg/ml. Solution for injection or infusion 10mg/ml.

Dose and administration:

In adults 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.

In the paediatric population the physician should prescribe the most appropriate formulation and strength according to weight and dose.

The following table summarises the recommended posology for children from 4 years of age and adolescents.

	Children (≥4 years) and adolescents ≥50 kg Administered in 2 equally divided doses	Children (≥4 years) and adolescents <50 kg Administered in 2 equally divided doses
Therapeutic dose range	50 - 200 mg/day	1 - 4 mg/kg/day
Recommended starting dose	50 mg/day (or 100 mg/day)*	1 mg/kg/day (or 2 mg/kg/day)*
Recommended maintenance dose	100 mg/day	2 mg/kg/day

* Based on physician assessment of need for seizure control.

Children (from 4 years of age) and adolescents weighing 50 kg or more

The recommended starting dose is 50mg/day. Brivaracetam may also be initiated at 100 mg/day based on physician assessment of need for seizure control. The dose should be administered in two equally divided doses, once in the morning and once in the evening. The recommended maintenance dose is 100 mg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 50 mg/day and 200 mg/day.

Children (from 4 years of age) and adolescents weighing less than 50 kg

The recommended starting dose is 1 mg/kg/day. Brivaracetam may also be initiated at 2 mg/kg/day based on physician assessment of need for seizure control. The dose should be administered in two equally divided doses, once in the morning and once in the evening.The recommended maintenance dose is 2 mg/kg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 1 mg/kg/day and 4 mg/kg/day.

Children less than 4 years

The safety and efficacy of brivaracetam in children aged less than 4 years have not yet been established.

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.

BNF therapeutic class / mode of action

Nervous system: antiepileptics

Licensed indication(s):

Adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy. [1] [2] [3]

Proposed use (if different from, or in addition to, licensed indication above):

As per licensed indication.

Brivaracetam currently has a RED RAG rating on LMMG for its previous licensed indication - 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

Course and cost: [3] [2] [1]

10mg white tab, 14=£34.64.

25mg grey tab, 56=£129.64.

50mg yellow tab, 56=£129.64.

75mg purple tab, 56=£129.64.

100mg green tab, 56=£129.64.

10mg/ml oral solution, 300ml=£115.83.

10mg/ml solution for injection/infusion, 10 x 5ml=£222.75.

Current standard of care/comparator therapies:

Within a submitted audit 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

Relevant NICE guidance:

NICE CG 137 [6] – this guideline was published prior to brivaracetam being licensed.

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. 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). Follow the MHRA safety advice on 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. Follow the MHRA safety advice on 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.

Background and context

Epilepsy is a disorder of the brain characterised by the recurrence of spontaneous, unprovoked seizures. [7]

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 with 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%. Coadministration with a high-fat meal slowed down the absorption rate (median tmax 3 h) and decreased the maximum plasma concentration (37 % lower) of brivaracetam, while the extent of absorption remained unchanged. [2]

Brivaracetam has a volume of distribution of 0.5L/kg; brivaracetam is weakly bound to plasma proteins (≤20%).

Brivaracetam is primarily eliminated by metabolism and excretion in the urine. More than 95% of a dose is excreted in the urine within 72hours 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 the previous LMMG review (2016). [8]

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.

The three studies were designated: **N01252** [9], **N01253** [10] and **N01358** [11]. 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.

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

Study Name	Brivaracetam Dose Regimens Assessed*
N01252	20mg/day**, 50mg/day or 100mg/day
N01253	5mg/day**, 20mg/day or 50mg/day
N01358	100mg/day or 200mg/day

*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.

Table 2 - Assessment of study interventions and comparators

Study	Intervention	Comparator	Primary outcome
N01252	Brivaracetam 20mg/day, 50mg/day or 100mg/day	Placebo	Percent reduction over placebo in the focal seizure frequency per week over the treatment period

N01253	Brivaracetam 5mg/day, 20mg/day or 50mg/day	Placebo	Percent reduction over placebo in the focal seizure frequency per week over the treatment period
N01358	Brivaracetam 100mg/day or 200mg/day	Placebo	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).

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

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

	Study N01252			Study N01253	
	Brivaracetam 50mg/day (n=99)	**Brivaracetam 100mg/day (n=100)**	**Placebo (n=100)**	**Brivaracetam 50mg/day (n=101)**	**Placebo (n=96)**
Primary endpoint					
Median POS frequency/week at baseline	1.80	2.0	2.1	2.9	2.6
Median reduction in focal seizure frequency/week over placebo, %	6.5%	12%	-	13%	-
p-value	p=0.261	p=0.037 (nominal)	-	p=0.025	-
Secondary endpoints					
≥50% responder rate, % (n/N)	27% (27/99)	36% (36/100)	20% (20/100)	33% (33/101)	17% (16/96)
Proportion of patients seizure free, % (n/N)	0%	4.0% (4/100)	0%	4.0% (4/101)	0%
p-value	p=0.339	p=0.023	-	p=0.008	

POS=partial-onset seizure

Table 4 - results of co-primary and secondary endpoint for licensed doses of brivaracetam in study N01358.

	Brivaracetam 100mg/day (n=252)	Brivaracetam 200mg/day (n=249)	Placebo (n=259)
Co-primary endpoints			
Median POS frequency/28 days at baseline	9.5	9.3	10.0
Median reduction in focal seizure frequency/28 days over placebo, %	23%	23%	-
p-value	p<0.001	p<0.001	-
≥50% responder rate, % (n/N)	39% (98/252)	38% 94/249)	22% (26/259)
p-value	p<0.001	p<0.001	-
Secondary endpoint			
Proportion of patients seizure free, % (n/N)	5.2% (13/252)	4.0% (10/249)	0.8% (2/259)

POS=partial-onset seizure

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.

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

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 28day 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.

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 28day 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.

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. No results have yet been published.

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%.

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%.

Paediatric population [2]

In children aged 4 years and older, partial onset seizures have a similar clinical expression to those in adolescents and adults. Experience with epilepsy medicines suggests that the results of efficacy studies performed in adults can be extrapolated to children down to the age of 4 years provided the paediatric dose adaptations are established and safety has been demonstrated. Doses in patients from 4 years of age were defined by weight-based dose adaptations which have been established to achieve similar plasma concentrations to the ones observed in adults taking efficacious doses.

A long-term, uncontrolled, open-label safety study included children (from 4 years to less than 16 years) who continued treatment after completing the PK study and children directly enrolled into the safety study. Children who directly enrolled received a brivaracetam starting dose of 1 mg/kg/day and depending on response and tolerability, the dose was increased up to 5 mg/kg/day by doubling the dose at weekly intervals. No child received a dose greater than 200 mg/day. For children weighing 50 kg or greater the brivaracetam starting dose was 50 mg/day and depending on response and tolerability, the dose was increased up to a maximum of 200 mg/day by weekly increments of 50 mg/day.

From the pooled open-label safety and PK studies in adjunctive therapy, 149 children with POS have received brivaracetam, of whom 116 have been treated for ≥6 months, 107 for ≥12 months, 58 for ≥24 months, and 28 for ≥36 months.

The efficacy and tolerability of brivaracetam in paediatric patients less than 4 years of age have not been established . Brivaracetam was evaluated in these patients in a short term openlabel pharmacokinetic study and an ongoing open-label extension study, in 16 subjects from 1 month to <4 years of age.

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. [8]

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. [8]

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%). [8]

From the pooled open-label safety and PK studies in adjunctive therapy, 149 children with POS have received brivaracetam, of whom 116 have been treated for ≥6 months, 107 for ≥12 months, 58 for ≥24 months, and 28 for ≥36 months.[2]

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]

System organ class	Frequency	Adverse reactions from clinical trials
Infections and infestations	Common	Influenza
Blood and lymphatic system disorders	Uncommon	Neutropenia
Metabolism and nutrition disorders	Common	Decreased appetite
Immune system disorders	Uncommon	Type I hypersensitivity
Psychiatric disorders	Common	Depression, anxiety, insomnia, irritability
	Uncommon	Suicidal ideation, psychotic disorder, aggression, agitation
Nervous system disorders	Very common	Dizziness, somnolence
	Common	Convulsion, vertigo
Respiratory, thoracic and mediastinal disorders	Common	Upper respiratory tract infections, cough
Gastrointestinal disorders	Common	Nausea, vomiting, constipation
General disorders and administration site conditions	Common	Fatigue

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.

The safety profile of brivaracetam observed in children was consistent with the safety profile observed in adults. In the open label, uncontrolled, long-term studies suicidal ideation was reported in 4.7 % of paediatric patients (more common in adolescents) compared with 2.4 % of adults and behavioural disorders were reported in 24.8 % of paediatric patients compared with 15.1 % of adults. The majority of events were mild or moderate in intensity, were non-serious, and did not lead to discontinuation of study drug. An additional adverse reaction reported in children was psychomotor hyperactivity (4.7%).

There are limited safety data from open-label studies in children from 1 month to <4 years of age. Limited data are available on neurodevelopment in children <4 years of age. No clinical data are available in neonates.

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]

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 oestrogen 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 oestradiol, 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 ≥50% responder rates in study N01252 (≥50 responder rates was the preferred primary endpoint for the EMA). [8]
2. No significant difference between brivaracetam and placebo in study N01252. [8]
3. Sub-group analyses of studies N01252 and N01253 showed no benefit for brivaracetam in patients taking concomitant levetiracetam. [8]
4. Studies were initiated before the ILAE definition of drug-resistant epilepsy was agreed. Therefore, patient 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). [8]
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. [8]
2. In a pooled analysis of the three pivotal trials, no differences in efficacy (measured as 50 % responder rate) was observed within the dose range of 50 mg/day to 200 mg/day when brivaracetam is combined with inducing or non-inducing AEDs. In clinical studies 2.5 % (4/161), 5.1 % (17/332) and 4.0% (10/249) of the patients on brivaracetam 50 mg/day, 100 mg/day and 200 mg/day respectively became seizure free during the 12-week treatment period compared with 0.5 % (2/418) on placebo.[2]
3. Improvement in the median percent reduction in seizure frequency per 28 days has been observed in patients with type IC seizure (secondary generalized tonic-clonic seizures) at baseline treated with brivaracetam (66.6 % (n=62), 61.2 % (n=100) and 82.1 % (n=75) of the patients on brivaracetam 50 mg/day, 100 mg/day and 200 mg/day respectively as compared to placebo 33.3 % (n=115)).[2]
4. All studies reviewed as part of the regulatory process were of good quality. [8]

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. Perampanel, zonisamide and lacosamide currently have an Amber0 RAG rating from LMMG 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. [8]

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. [8]

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. [8]

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 16years 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. [8]

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 wold be negligible when the cost of monitoring therapy was considered. Therefore, the cost-minimisation analysis focused on the maintenance costs only. [8]

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. [8]

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. [8]

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: [12]

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Brivaracetam	**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**

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Lacosamide	100mg – 200mg p.o. b.d.	50mg tablets x 14 = £10.81. 100mg tablets x 56 = £86.50. 150mg tablets x 56 = £129.47. 200mg tablets x 56 = £144.16. 10mg/ml syrup x 200ml = £25.74. 10mg/ml infusion x 20ml = £29.70.	£1,125 – £1,874
This table does not imply therapeutic equivalence of drugs or doses.			

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:

On the initial application (for use in prior adults / adolescents licensed indication)the applicant stated that they expected twenty patients per year across the Lancashire footprint to be treated with brivaracetam in their organisation. This figure is supported by an audit in Royal Preston Hospital from August 2017-18 which identified 14 patients being prescribed brivaracetam (age range 12-58) – in all but one case it was used as 4th line or later.

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. [8]

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 = 20 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 – £1499 = £186 (in favour of brivaracetam)

Difference in cost at the maximum dose =

£1,685 – £1,874 = -£189 (in favour of brivaracetam)

Difference in cost at the lowest licensed dose =

£1,685 – £1,125 = £560 (in favour of lacosamide)

The SMC conducted an economic analysis (discussed above) which concluded that when additional costs were taken in to 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 / alternative therapy to drug resistant patients.

The SMC and AWMSG have approved brivaracetam for restricted use.

Pan Mersey APC (October 2018) have given brivaracetam an Amber initiated status - requires specialist initiation of prescribing. Prescribing to be continued by the specialist until stabilisation of the dose is achieved and the patient has been reviewed by the specialist.

GMMMG have given brivaracetam a Green (following specialist initiation) status - suitable for on-going prescribing within primary care. Little or no monitoring is required. Transfer of prescribing should occur after initiation and an initial review (unless specified) in secondary care.

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. [13]

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area in patients with treatment resistant/refractory epilepsy. [8]

References

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[3] UCB Pharma Limited, “Summary of Product Characterisitcs - Briviact 10 mg/ml solution for injection/infusion,” 22 May 2019 [Online]. Available: https://www.medicines.org.uk/emc/product/1967/smpc

[4] Scottish Medicines Consortium, “Bivaracetam 10mg, 25mg, 75mg, 100mg film-coated tablets; 10mg/mL oral solution; 10mg/mL solution for injection/infusion (Briviact) SMC 2113 https://www.scottishmedicines.org.uk/medicines-advice/brivaracetam-briviact-abbreviated-smc2113/

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[6] Epilepsies: diagnosis and management NICE CG137 Last Updated April 2018 https://www.nice.org.uk/guidance/cg137

[7] Briviact EPAR 2015 https://www.ema.europa.eu/en/documents/assessment-report/briviact-epar-public-assessment-report_en.pdf

[8] Scottish Medicines Consortium brivaracetam (Briviact) SMC 1160/16 https://www.scottishmedicines.org.uk/medicines-advice/brivaracetam-briviact-fullsubmission-116016/
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[11] A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Klein P et al; Epilepsia. 2015 Dec;56(12):1890-8.
[12] NHS Electronic Drug Tariff May 2019
[13] Definition of Drug-Resistant Epilepsy (Patrick Kwan) Epigraph VOL. 12 ISSUE 1, Winter 2010

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR