AWMSG Secretariat Assessment Report – Limited submission

Brivaracetam (Briviact®▼) 10 mg, 25 mg, 50 mg, 75 mg and 100 mg film-coated tablets; 10 mg/ml oral solution; 10 mg/ml solution for injection/infusion

Company: UCB Pharma Ltd

Licensed indication under consideration: As adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in children from 4 to ≤ 15 years of age with epilepsy. Brivaracetam (Briviact®) should be restricted to use in the treatment of patients with refractory epilepsy, who remain uncontrolled with, or are intolerant to, other adjunctive anti-epileptic medicines.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Date of licence extension: 11 July 2018

Comparator(s)

The comparators included in the company submission are:

- eslicarbazepine acetate (Zebinix®)
- lacosamide (Vimpat®)
- oxcarbazepine (Trileptal®)
- zonisamide (Zonegran®)

Limited submission details

- The limited submission criteria were met based on a minor licence extension and anticipated minimal budgetary impact in NHS Wales

Clinical effectiveness

- Brivaracetam (Briviact®) has previously been recommended by the All Wales Medicines Strategy Group (AWMSG) for restricted 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 adult and adolescent patients from 16 years of age with epilepsy.
- This submission covers a licence extension to include children aged ≥ 4 to ≤ 15 years.
- Treatment choice in epilepsy is guided by a number of factors including patient co-morbidities, concurrent medications, medicine tolerability and formulation(s) available. AWMSG previously recommended lacosamide as an option for the same indication under consideration. Clinical experts in Wales have confirmed that in general they would expect to use brivaracetam as third-line treatment; that is, after failure of monotherapy and first-line adjunctive therapy. It is therefore

expected that brivaracetam would potentially displace lacosamide, zonisamide, oxcarbazepine or eslicarbazepine acetate (the latter three are licensed for children above 6 years of age). Brivaracetam is reported to be useful in people who have responded to levetiracetam but had behavioural or other side effects that have led to its cessation.

- The paediatric licence extension was based on the extrapolation of efficacy data from clinical studies in patients aged 16 years and above, with additional supportive data regarding the dosage and safety of brivaracetam in children aged 4 years and above. The European Medicines Agency has endorsed the extrapolation of efficacy results of anti-epileptic medicines in adults to children via a reflection paper on extrapolation in paediatric medicine development, and a guideline on the clinical investigation of epilepsy-specific medicinal products.
- Three multicentre, double-blind, randomised, placebo-controlled phase III studies in patients aged 16 to ≤ 80 years to assess efficacy of brivaracetam, have been assessed. Pooled results from 1,567 patients showed statistically significant reductions in baseline-adjusted POS frequency of 19.5% (50 mg/day), 24.4% (100 mg/day) and 24.0% (200 mg/day) over placebo. In addition, the percentage of treated patients with a reduction in seizure frequency of at least 50% ranged from 34.2% (50 mg/day) and 37.8% (200 mg/day) to 39.5% (100 mg/day) compared to 20.3% for the placebo group.
- There is no direct head-to-head comparative evidence between brivaracetam and the four comparators so the company conducted a Bayesian network meta-analysis of relevant randomised controlled studies of adjunctive therapy of POS in adults. The results showed that brivaracetam had comparable efficacy to eslicarbazepine acetate, lacosamide, oxcarbazepine and zonisamide, in achieving at least 50% reduction in seizure frequency from baseline.
- Pooled safety and tolerability data from one completed and one on-going study, in 149 patients aged 4 to ≤ 15 years, showed that observations were as expected for the paediatric population; most adverse events were either mild or moderate and no new safety concerns were identified. The Committee for Medicinal Products for Human Use concluded that the safety profile observed in patients aged 4 years and over was generally consistent with that seen in adults.

Budget impact

- The company estimates that 185 children (aged ≥ 4 to ≤ 15 years) are eligible for brivaracetam treatment in NHS Wales in the first year, based on population data for Wales, prevalence and incidence data for the UK, and assumes that 35% of people with epilepsy have POS and 30% of these would need adjunctive therapy.
- The cost of treatment differs according to the weight of the patient. To account for this the annual cost per patient for brivaracetam and each of the comparators was calculated using median weight data for each age within the range ≥ 4 to ≤ 15 years and Welsh population size data for the relevant age range.
- Based on the company's market share projections, brivaracetam is assumed to partly displace all four comparators (lacosamide 3.5%; zonisamide 34.9%; oxcarbazepine 8.6%; eslicarbazepine 53.0%), with an estimated four patients likely to be prescribed brivaracetam in Year 1 based on an anticipated uptake of 2% increasing to 25 patients in Year 5 based on an anticipated uptake of 8%. The company estimates that this will result in net medicine acquisition cost savings of £856 in Year 1 to £7,007 in Year 5.
- Whilst there are some limitations in the company's estimate which could result in a net cost, the overall budgetary impact is anticipated to be minimal.

Additional information

- AWTTC is of the opinion that, if recommended, brivaracetam (Briviact®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

Evidence search

Date of evidence search: 8 August 2018
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Brivaracetam (Briviact®) 10 mg, 25 mg, 50 mg, 75 mg and 100 mg film-coated tablets, 10 mg/ml oral solution, 10 mg/ml solution for injection/infusion. Reference number: 3387. November 2018.

Appendix: Previous AWMSG secretariat assessment report (published July 2016)

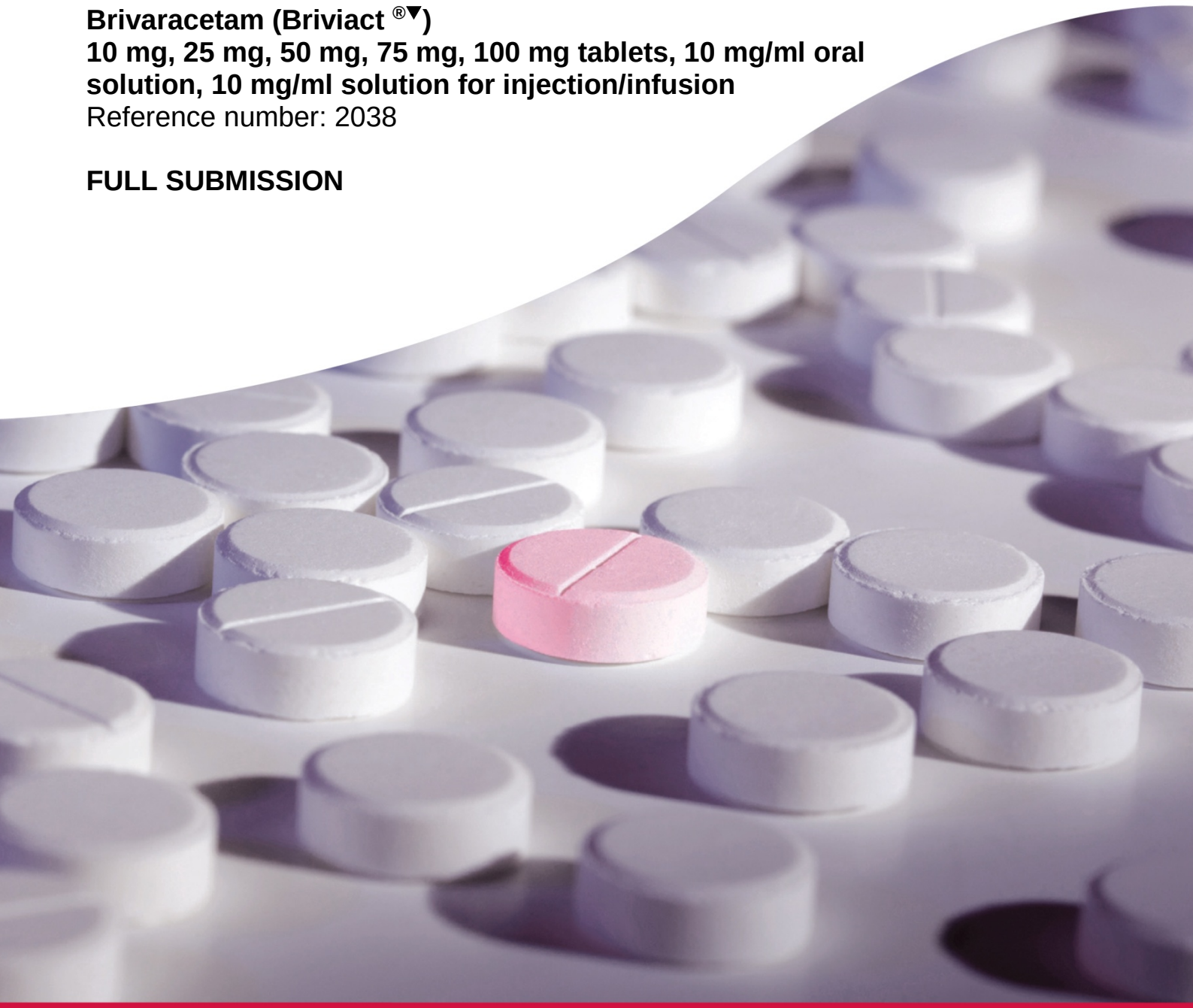
This report was published as part of a previous AWMSG appraisal of brivaracetam (Briviact®) (Advice number 2516). The advice from this appraisal has been superseded by advice number 2318. The original appraisal documentation is included here for completeness.

All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Brivaracetam (Briviact ®▼)
10 mg, 25 mg, 50 mg, 75 mg, 100 mg tablets, 10 mg/ml oral solution, 10 mg/ml solution for injection/infusion
Reference number: 2038

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Brivaracetam (Briviact®▼) 10 mg, 25 mg, 50 mg, 75 mg, 100 mg tablets, 10 mg/ml oral solution, 10 mg/ml solution for injection/infusion

This assessment report is based on evidence submitted by UCB Pharma Ltd.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Brivaracetam (Briviact®▼) is indicated as adjunctive therapy in the treatment of partial-onset seizures (POS) with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy[1].
Dosing	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[2-4].
Marketing authorisation date	14 January 2016[2-4].

2.0 DECISION CONTEXT

2.1 Background

Epilepsy is a chronic neurological disorder characterised by recurring, unprovoked seizures. The disorder affects over 600,000 (based on 2010 figures) people in the UK[5]. Partial-onset (focal) seizures (POS) account for approximately 60% of epilepsy cases. POS originate in networks limited to one hemisphere and may remain localised or propagate into secondary generalised seizures[6]. Primary treatment involves monotherapy with anti-epileptic drugs (AEDs) with the option of adjunctive therapy where primary treatment is unsuccessful[7]. Despite the introduction of third generation AEDs, the condition remains uncontrolled in approximately 35% of patients[8,9].

Brivaracetam is a new AED that binds to synaptic vesicle protein 2A and modulates neurotransmitter release, a mechanism believed to confer anticonvulsant activity[10]. Brivaracetam is a new treatment option for adjunctive therapy in patients with uncontrolled epilepsy[1].

2.2 Comparators

The comparators included in the company submission were:

- eslicarbazepine acetate (Zebinex®)
- lacosamide (Vimpat®)
- perampanel (Fycompa®)
- zonisamide (Zonegran®▼)

2.3 Guidance and related advice

- NICE. Clinical Guideline 137. Epilepsies: diagnosis and management (2012)[7].
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults (2015)[11].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of eslicarbazepine acetate (Zebinex®)[12] and perampanel (Fycompa®)[13].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submitted three randomised placebo-controlled trials comparing brivaracetam with placebo that measured efficacy variables as their primary endpoints[14-16]; a pooled analysis of these trials is presented here. In the absence of any head-to-head trials between brivaracetam and other AEDs licensed for the adjunctive treatment of POS, a systematic review and network meta-analysis (NMA) were carried out to estimate the comparative efficacy and safety of brivaracetam[1].

3.1.1 Clinical effectiveness of brivaracetam versus placebo

Pooled efficacy and safety analyses were submitted by the company using data from three placebo-controlled, double-blind, fixed dose randomised controlled trials: N01252, N01253 and N01358[1,14-16]. All patients included in the pooled analyses were aged between 16 and 80 years with uncontrolled POS and were receiving one or two concomitant AEDs at a stable and optimal dose. Following an eight week baseline period, brivaracetam or placebo was administered twice daily for a treatment duration of 12 weeks. The daily dose of brivaracetam ranged from 5 mg to 200 mg/day across all three studies; the pooled analysis only included patients who were randomised to the licensed daily dose of 50 mg, 100 mg or 200 mg. Patients who were taking concomitant levetiracetam were excluded from the pooled analysis. Two of the individual clinical studies (N01252 and N01253) included patients taking levetiracetam concurrently; there was no observed benefit of brivaracetam versus placebo in this group of patients. Study N01358 excluded patients who were taking concomitant levetiracetam.

The primary endpoints were the percent reduction in POS frequency over placebo and the 50% responder rate based on a 50% reduction in POS frequency from baseline to the 12 week treatment period. The pooled analysis demonstrated that brivaracetam 50 mg, 100 mg and 200 mg/day resulted in a statistically significant reduction in the 28 day adjusted POS frequency over placebo. Significantly higher 50% responder rates were observed across all treatment groups compared to placebo (Table 1)[1]. Seizure freedom rate (secondary outcome, defined as freedom from all seizure types [Types I, II and III]) was increased for the 50 mg, 100 mg and 200 mg brivaracetam treatment groups over placebo (Table 1).

Table 1. Efficacy of brivaracetam against placebo in reducing seizure frequency in pooled analysis

	Placebo	Brivaracetam (daily dose)		
		50 mg	100 mg	200 mg
n (total 1,160)	418	161	332	249
% reduction in POS frequency over placebo[†]	-	19.5 (p = 0.00148)	24.4 (p <0.00001)	24.0 (p <0.00001)
≥50% responder rate[§] (%)	20.3	34.2 (p = 0.00150)	39.5 (p <0.00001)	37.8 (p <0.00003)
Seizure freedom rate * (%)	0.5	2.5	5.1	4.0

POS: partial onset seizures.
[†] For studies N01252 and N01253 post hoc transformation adjusted 7-day to 28-day seizure frequencies.
[§] Patients with a 50% or greater reduction in POS frequency from baseline were defined as a responder, whether or not the patient completed the treatment period.
* The seizure freedom rate from all seizure types (I, II and III).

3.1.2 Indirect comparison of brivaracetam with comparator treatments

In the absence of trials directly comparing the clinical effectiveness of brivaracetam with relevant comparators, the company estimated comparative efficacy and safety from an NMA. A systematic review was conducted to identify relevant evidence; study inclusion criteria were randomised controlled trials (or open-label extension studies) of adult epilepsy patients with partial seizures including simple partial, complex partial, and secondary generalised tonic/clonic seizures. Trials included a range of AEDs, including (but not limited to) brivaracetam and the comparators chosen by the company. The review identified 79 relevant studies; of these, five evaluated brivaracetam, five evaluated eslicarbazepine, five evaluated perampanel, three evaluated lacosamide and seven evaluated zonisamide[1]. For all studies, the AEDs were used in an adjunctive setting for a minimum of eight weeks.

Separate NMAs were conducted for two efficacy outcomes and one safety outcome: 50% responder rate, seizure freedom rate and discontinuation due to treatment-emergent adverse events. For each AED, data for differing doses within the licensed dose range was pooled. Outcomes for brivaracetam excluded patients taking concomitant levetiracetam.

The results estimated that the probability of achieving seizure freedom was greater for brivaracetam than for the comparators, but the difference was not statistically significant (Table 2). Similarly, brivaracetam treatment also gave the highest probability of achieving a 50% response rate (Table 2), but the difference between brivaracetam and the comparators was not statistically significant[1].

Table 2. Probability of achieving at least 50% response rate and seizure freedom for brivaracetam, placebo and comparators

	Probability of achieving seizure freedom*	Probability of achieving at least 50% response rate†
Treatment	**Median absolute probability [95% CrI]**	
Placebo	0.013 [0.004, 0.043]	0.176 [0.082, 0.339]
Brivaracetam	0.065 [0.012, 0.334]	0.355 [0.176, 0.585]
Eslicarbazepine acetate	0.032 [0.008, 0.127]	0.330 [0.162, 0.555]
Lacosamide	0.030 [0.006, 0.142]	0.308 [0.144, 0.536]
Perampanel	0.035 [0.008, 0.147]	0.296 [0.138, 0.516]
Zonisamide	0.018 [0.004, 0.072]	0.335 [0.165, 0.564]

CrI: credible interval
* Defined as seizure freedom from all seizure types and calculated for patients who completed the trial assessment period. Network meta-analysis informed by 42 studies.
† At least a 50% reduction in monthly POS frequency from baseline to the treatment period or maintenance period. Data from 58 studies for 12 treatments provided evidence in the network meta-analysis.

3.1.3 Safety

Pooled safety analysis of studies N01252, N01253 and N01358 provided the basis for the adverse drug reactions (ADRs) in the brivaracetam SPCs[2-4]. In the brivaracetam group, 6.7% of patients discontinued treatment due to treatment-emergent adverse events (TEAEs) compared with 3.9% in the placebo group. Severe TEAEs were reported for 5.4% of brivaracetam patients with the most frequent system organ class being nervous system disorders (20 out of 59 patients)[10]. Somnolence, dizziness and fatigue were reported more frequently in the brivaracetam treatment group (14.3%, 11.0% and 8.2% of subjects respectively) compared with placebo (8.5%, 7.2% and 3.7% of subjects). The incidence of fatigue and somnolence appeared dose-related[10].

The NMA found no significant difference in the probability of discontinuing treatment due to TEAEs for the brivaracetam treatment group compared with any of the chosen comparators. The odds of discontinuation of treatment due to TEAEs were significantly higher for all of the comparators than for placebo (OR [95%CrI]: 2.58 [1.68, 4.02], 3.01 [1.76, 5.43], 2.10 [1.25, 3.64], 2.26 [1.37, 3.88] for eslicarbazepine acetate, lacosamide, perampanel, and zonisamide respectively). The odds of discontinuation were also greater for brivaracetam than for placebo, but this difference was not statistically significant (OR [95%CrI]: 1.84 [0.88, 4.06])[1].

3.2 AWTTC critique

- Based on advice from Welsh clinicians and market share data, the company determined lacosamide, perampanel, eslicarbazepine acetate and zonisamide as the most appropriate comparators to brivaracetam. AEDs licensed for monotherapy in addition to adjunctive treatment were not considered appropriate by the company as they would be used at an earlier stage in the treatment pathway. The exception was zonisamide, which was included by the

company based on clinical expert advice that it is frequently used in Wales as an adjunctive treatment[1].

- Results of a systematic review and NMA suggest uncertainty in whether brivaracetam is more effective than the chosen comparators. The probability of seizure freedom or at least 50% response was greater with brivaracetam than with any of the comparators, but these differences were not statistically significant. The trials included in the NMA appear to be relevant to the appraised indication: all patients had partial seizures, and interventions were used in the adjunctive setting. The NMA was based on a systematic review which was carried out in November 2014 and therefore excludes any evidence published after this date.
- The evidence submitted by the company to support the efficacy and safety of brivaracetam covers a maximum treatment period of 12 weeks. However, evidence from patients treated with brivaracetam as part of long-term open-label, single-arm follow up studies[17] (published during the compilation of this report) suggests that brivaracetam has similar efficacy and tolerability long-term to that reported in the pooled analysis (treatment period: 12 weeks) presented here. Across all long-term follow up studies, 6-, 12-, 24-, and 60-month retention rates with brivaracetam were 91.0%, 79.8%, 68.1%, and 54.4%, respectively[17].
- The Committee for Medicinal Products for Human Use commented that the safety profile of brivaracetam was considered relatively benign for an AED across the therapeutic dose range, with most ADRs reported being mild to moderate in intensity[10].
- Brivaracetam has a favourable tolerability profile and does not need to be up-titrated slowly to the minimal therapeutic dose. Welsh clinical experts have commented that this has practical benefits for patients and that up-titration of existing AEDs can cause difficulties. Brivaracetam also has a low interaction potential[2].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] includes a cost-utility analysis (CUA) comparing brivaracetam with eslicarbazepine acetate, lacosamide, perampanel, and zonisamide in the treatment of patients aged 16 years and over with POS who have not responded to monotherapy and require adjunctive therapy. In Europe, 17 AEDs have licensed indications that include both monotherapy and adjunctive therapy. However, only six of these are licensed solely as adjunctive therapies; three of which were selected for inclusion in the model. Pregabalin was excluded on the advice of company-sourced clinical expert opinion, vigabatrin on the grounds that it is only licensed for resistant POS, and retigabine due to its small market share in Wales (0.55%). Zonisamide was included as a fourth comparator, despite it also being licensed as a monotherapy, on the basis that it is frequently used as an adjunctive therapy in Wales, according to Welsh clinicians.

The CUA takes the form of a discrete event simulation (DES) which adopts an NHS Wales and Personal Social Services perspective and a two year time horizon. Costs and benefits are discounted at 3.5% per annum. The model uses a simulated cohort of 50,000 patients, whose baseline characteristics are sampled from brivaracetam pooled efficacy data[18] (age, sex, seizure frequency per month) and Office of National Statistics data (ethnicity)[19]. The model includes five lines of adjunctive AEDs. Patients are initially randomly allocated to brivaracetam or a comparator AED. Patients may discontinue a line of therapy due to lack of efficacy or the occurrence of an adverse event. Efficacy and discontinuation probabilities are taken from the NMA conducted. If discontinuation

occurs, patients are subsequently randomly assigned to another available AED. Patients can however be given more than one adjunctive therapy within the model. If the response to a medicine is not deemed acceptable, the most recent AED will be swapped or a further drug will be added to the regimen, depending on the number of adjunctive AEDs already attempted: if the patient is on two AEDs and has tried three adjunctive treatment lines or more, another AED is added without replacement (i.e. fourth or fifth line adjunctive therapy). A patient may also be assessed for surgery after two or more adjunctive AEDs have been trialled. Estimates for the proportion of patients undergoing assessments (7.5%), eligible for surgery (30%) and whose surgery is successful (50%) have been guided by clinical expert opinion. A cured patient remains seizure free until death. Age-specific mortality risks of the general population are used at baseline, and are adjusted to model the relative all-cause mortality of patients with active epilepsy and those who are seizure free. Thus, mortality risk status changes in accordance with treatment responses over time. The model imposes a ceiling age of 100 years.

In addition to those already mentioned, the model is structured using a number of assumptions, including:

- No interaction between the treatment effects of adjunctive therapy. AED efficacy is not affected by response or discontinuation of previously received AEDs.
- Patients receive treatment effects and associated utility as soon as a treatment is commenced.
- Adverse events (AEs) that result in discontinuation only occur during the titration and response assessment periods.
- Titration drug costs are incurred as a one-off costs at the start of treatment, to mirror dispensing practices.

The model incorporates costs associated with drug acquisition, monitoring, surgery and AEs. Monitoring costs are influenced by whether or not patients are seizure free, and are guided by NICE clinical guideline CG137[7,20] . Costs associated with AEs experienced during the titration and response assessment periods are calculated by valuing resource utilisation estimates apportioned to the AEs experienced in the brivaracetam safety trials. Late-onset AEs not leading to discontinuation are not included in the model. Unit costs are sourced from MIMS[21], NHS Reference Costs[22] and the Personal Social Services Research Unit[23].

Response-based utilities are applied from treatment initiation. Different utilities are assigned to patients with seizure freedom, ≥50% reduction in seizures, and <50% reduction in seizures (no response). No utility decrements have been modelled for early-onset adverse events, given that these are likely to be short-lived as treatment is immediately withdrawn.

Univariate and probabilistic sensitivity analyses (PSA) and a number of scenario analyses have been conducted to test the influence of the uncertainty of individual parameters and structural assumptions on the robustness of the base case results. The scenarios test, amongst other factors, the impact of altering the time horizon, the source for utility values and the maintenance dosing for lacosamide.

4.1.2 Results

The results of the base case pair-wise comparisons are detailed in Table 3. The comparisons reveal that when compared with perampanel and esclicarbazine acetate, brivaracetam is both less costly and more effective (i.e. it dominates). If a willingness-to-pay (WTP) threshold of £20,000 per QALY gained is applied, brivaracetam can be considered a cost-effective treatment when compared with lacosamide and zonisamide.

Table 3. Results of the base case pair-wise cost-effectiveness analyses

	Brivaracetam (BRV)	Comparator treatment	Difference
Brivaracetam vs lacosamide			
Total costs	£5,978	£5,880	**£98**
Total life-years	1.980	1.980	**0**
Total QALYs	1.546	1.536	**0.010**
ICER (£/QALY gained)	**£10,147**		
Brivaracetam vs perampanel			
Total costs	£5,978	£6,238	**-£260**
Total life-years	1.980	1.980	**0**
Total QALYs	1.546	1.532	**0.014**
ICER (£/QALY gained)	**Brivaracetam dominant**		
Brivaracetam vs eslicarbazepine acetate			
Total costs	£5,978	£6,115	**-£137**
Total life-years	1.980	1.981	**-0.001**
Total QALYs	1.546	1.537	**0.009**
ICER (£/QALY gained)	**Brivaracetam dominant**		
Brivaracetam vs zonisamide			
Total costs	£5,978	£5,903	**£75**
Total life-years	1.980	1.979	**0.001**
Total QALYs	1.546	1.532	**0.014**
ICER (£/QALY gained)	**£5,417**		
ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year.			

The results of the univariate analyses reveal that the ICERs produced are highly sensitive to differences in relative response rates between the treatments used in the model, and to changes in the cost of monitoring. These heightened sensitivities are a result of the similarities between the costs and effectiveness of the treatments.

The results of the probabilistic sensitivity analyses are detailed in Table 4. The probability of brivaracetam being cost-effective at WTP thresholds of £20,000 and £30,000 per QALY gained is high when compared with perampanel. However, there is a higher degree of uncertainty associated with the other pair wise comparisons. Table 5 provides more detailed information relating to the proportion of simulations that fall within each quadrant of the cost effectiveness plane.

Table 4. Results of the probabilistic sensitivity analyses

Pair wise comparison	Probability of the treatment pathway containing Brivaraetam being cost-effective at a WTP threshold of:	
	£20,000	£30,000
Brivaracetam vs lacosamide	**57%**	**60%**
Brivaracetam vs perampanel	**81%**	**83%**
Brivaracetam vs eslicarbazepine acetate	**51%**	**52%**
Brivaracetam vs zonisamide	**52%**	**55%**
WTP: willingness to pay		

Table 5. Proportion of simulations within each quadrant of the cost effectiveness plane

Pair wise comparison	Quadrant			
	North east (+ cost/ + QALY)	South east (- cost/ + QALY)	South west (-cost/ - QALY)	North west (+ cost/ - QALY)
Brivaracetam vs lacosamide	38%	31%	9%	22%
Brivaracetam vs perampanel	17%	63%	13%	7%
Brivaracetam vs eslicarbazepine	31%	13%	39%	17%
Brivaracetam vs zonisamide	24%	40%	2%	35%
QALY: quality adjusted life year				

The majority of scenario analyses conducted resulted in no change to dominance findings and ICERs remained below £20,000. Those scenarios which yielded the most notable results are detailed in Table 6.

Table 6. Results of the scenario analyses

Scenario	ICER	Plausibility
Time horizon increased to 5 years: a) Brivaracetam vs lacosamide b) Brivaracetam vs eslicarbazepine acetate c) Brivaracetam vs zonisamide	a) £30,409 b) £1,555 c) £18,798	While a two year time horizon does avoid the need for extensive extrapolation, it is also limited given that epilepsy is a non-curable condition. A five year time horizon could therefore be considered more plausible in this instance. That said, a time horizon greater than five years is arguably even more plausible.
Alternative utility values: a) Brivaracetam vs lacosamide b) Brivaracetam vs zonisamide	a) £15,913 b) £8,537	The base case utilities are derived from patients receiving monotherapy. These alternative values are instead derived from patients commenced on adjunctive therapy, and are therefore a plausible alternative to the base case.
Alternative maintenance dosing of lacosamide, from 300 mg/day to 250 mg/day: a) Brivaracetam vs lacosamide	a) £24,578	Dose is titrated according to response, up to a maximum of 400 mg/day[24]. The WHO daily defined dose is 300 mg/day[25].
ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year		

4.1.3 AWTTC critique

The results of the base case CUA presented by the company suggest that brivaracetam can be considered a cost effective treatment option when compared with eslicarbazepine acetate, lacosamide, perampanel, and zonisamide. However, while the submission is characterised by a number of strengths, it also has limitations. Notably, model sensitivity to variations in parameter inputs, the choice of comparators, and the time horizon used, amongst other factors, all contribute to uncertainty surrounding these results.

Strengths of the submission include:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- The use of DES facilitates the modelling of a full event history for each patient, including changes to characteristics over time.
- A variety of sensitivity and scenario analyses have been conducted to test the robustness of the model parameter changes.

Limitations of the submission include:

- The company have limited the comparators used to generate ICERs to epilepsy medications which are solely indicated for adjunctive therapy (i.e. not both monotherapy and adjunctive therapies). However, the model includes a wider range of comparators in the treatment pathways. It is uncertain whether the most appropriate comparators have been included in the ICER calculations; and what ICERs may have been produced if brivaracetam had been compared with other treatments.
- The market shares used in the model for all medicines, not only those selected as comparators, are based on English prescribing data[26]. It is uncertain how reflective these data are of prescribing practices in Wales.
- The two year time horizon of the model does not capture all relevant costs and consequences; epilepsy is a chronic condition that requires long term treatment. Scenario analyses reveal that increasing the timeline to five years significantly increases the ICERs. AWTTC analysis also found that with longer time horizons the cost-effectiveness of brivaracetam reduces. For example, over a 10 year time horizon when comparing brivaracetam with lacosamide, the ICER increases to £68,680 per QALY gained; when comparing brivaracetam with zonisamide, the ICER increases to £31,114 per QALY gained.
- Given that all titration costs are applied at the start of the titration period, and that brivaracetam is the only treatment not associated with a titration period/costs, this may introduce some bias in favour of brivaracetam.
- The utility values used in the base case are taken from a study focused on monotherapy, and may therefore not be reflective of the utilities of patients receiving adjunctive therapy. The uncertainty associated with this has however been explored via scenario analyses (see Table 6).
- The use of NMA to guide efficacy and discontinuation probabilities within the model introduces an element of uncertainty.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any published studies evaluating the cost-effectiveness of brivaracetam.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company have estimated that there will be 4,426 patients aged 16 years or over with partial onset seizures requiring adjunctive therapy in 2016. This estimate is based on ONS population statistics[27,28] and Welsh-specific prevalence data for epilepsy published by the Joint Epilepsy Council[5]. The prevalence of POS has been calculated using data from a prospective population-based cohort study of epilepsy published in 1990[29]. The proportion of these patients requiring adjunctive therapy has been taken from an article published in 2000[8]. The same data sources have been used to estimate incidence. To calculate the number of patients who require adjunctive therapy in Wales, the company have combined the incidence and prevalence estimates, and have applied a 0.30% annual population growth rate[30] together with a 1% annual epilepsy-adjusted mortality rate. An assumed market share of [commercial in confidence text removed] in year one, increasing to [commercial in confidence text removed] in year five is further applied to estimate the number of patients likely to be prescribed brivaracetam in Wales. No sensitivity analyses have been performed.

5.1.2 Results

The budget impact analyses are presented in Table 7. The introduction of brivaracetam is reported to be associated with costs savings ranging from £8,627 in 2016 to £11,351 in 2020.

Table 7. Net budget impact (¶¶ indicates commercial in confidence data)

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Number of eligible patients (Indication covered in this submission)	4,426	4,439	4,453	4,466	4,479
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Treated patients	¶¶	¶¶	¶¶	¶¶	¶¶
Total cost in current market without brivaracetam	£8,685,309	£8,715,098	£8,743,739	£8,772,474	£8,801,302
Total cost in new market with brivaracetam	£8,676,682	£8,705,123	£8,732,707	£8,762,145	£8,789,951
Net cost	**-£8,627**	**-£9,975**	**-£11,032**	**-£10,328**	**-£11,351**
Cumulative net cost	**-£8,627**	**-£18,602**	**-£29,634**	**-£39,963**	**-£51,314**

5.1.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact. The company have also factored in population growth and mortality into the calculations.
- Kwan and Brodie[8] suggest that at least 30% of patients with epilepsy require adjunctive therapy. The use of 30% in the prevalence calculations may therefore underestimate the number of patients treated. Some sensitivity analyses focused on higher estimates would have been beneficial.
- The budget impact model is limited to acquisition costs only of the base and adjunctive AEDs only; other resource use is not included (e.g. monitoring costs and costs associated with adverse events).
- The estimates for uptake are based on company assumptions. Furthermore, the medicines used to calculate the effects of market share displacement are limited to the four comparators used for the CUA. These projections are therefore possibly limited in scope.
- Lack of any sensitivity analyses prevents exploration of the effects of changes to model parameters on the budget impact.
- Collectively, the budget impact calculations are subject to uncertainty.

5.2 Comparative unit costs

Table 8 provides examples of medicines used as adjunctives to treat POS in patients aged 16 years and over.

Table 8. Examples of acquisition costs for epilepsy medicines.

Regimens	Example doses	Approximate costs per patient (per annum)
Medicines licensed for adjunctive therapy only		
Brivaracetam (Briviact®) tablets	50–200 mg daily	£1,815
Perampanel (Fycompa®) tablets	4–12 mg daily	£1,960
Eslicarbazepine (Zebinix®) tablets	800 mg–1.2 g daily	£1,768–£2,584
Lacosamide (Vimpat®) tablets	200–400 mg daily	£1,211–£2,018
Retigabine (Trobalt®) tablets	600 mg–1.2 g daily	£1,028–£1,788
Pregabalin capsules	300–600 mg daily	£451–£901
Tiagabine (Gabitril®) tablets	15–45 mg daily	£625–£1,717
Vigabatrin (Sabril®) tablets	1.0–3.0 g daily	£355–£977
Clobazam tablets	20–60 mg daily	£77–£229
Medicines licensed for monotherapy and adjunctive therapy		
Zonisamide (Zonegran®) capsules	300–500 mg daily	£1,254–£2,070
Gabapentin capsules or tablets	900 mg–3.6 g daily	£42–£331
Levetiracetam tablets	1.0–3.0 g daily	£45–£122
Oxcarbazepine (Trileptal®) tablets	600 mg–2.4 g daily	£312–£1,170
Topiramate tablets	200–400 mg daily	£98–£183
Sodium valproate (Epilim®) tablets	1.0–2.5 g daily	£154–£366
Lamotrigine tablets	100–700 mg daily	£13–£79
See relevant SPCs for full licensed indications and dosing details. Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of April 2016[21], assuming wastage. They are indicative of minimum and maximum costs; which do not necessarily reflect minimum and maximum dosing. This table does not imply therapeutic equivalence of drugs or the stated doses. The cost reported for brivaracetam differs slightly from that used in the model given that a prescription cost approach has been adopted in calculating these costs.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, brivaracetam for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

The company do not anticipate that brivaracetam will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 14th April 2016
Date range of evidence search: No date limits were applied to database searches.

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