NHS Bedfordshire Clinical Commissioning Group

NHS Luton Clinical Commissioning Group

BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)

September 2017
Review:
September 2020

Bulletin 257: Brivaracetam for Epilepsy

JPC Recommendations:

- Brivaracetam is supported for use within its marketing authorisation (as an 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) in patients who have refractory epilepsy and are intolerant to levetiracetam (prescribed as the generic preparation) or have co-morbidities/receiving interacting medication which would preclude its use.

- Treatment must be initiated by the specialist neurology service and may be continued by GPs.

New Medicine Review – Bulletin - Brivaracetam

Medicine	Brivaracetam (Briviact)
Document status	*Final*
Date of last revision	20th September 2017
Proposed Sector of prescribing	Specialist initiation in neurology and continuation in primary care when the patient is stable.
Introduction	Epilepsy is a common neurological disorder characterised by recurring seizures [1]. There are at least 40 different seizure types and individuals may have one or several different types [2]. Focal (partial-onset) seizures are the most common type in adults: seizures arise from a focus within the cerebral cortex [3]. Partial-onset seizure types include [3]: 1. Simple partial seizures, which occur without impairment of consciousness or awareness 2. Complex partial seizures, where the major feature is altered cognition 3. Secondary generalised tonic-clonic seizures, where the person has a bilateral convulsive seizure The incidence of epilepsy in the UK is estimated to be 50 per 100,000 per year and the prevalence of active epilepsy is estimated to be 0.97%, or 1 in 103 people.[1, 2] Epilepsy affects approximately 260,000 to 416,000 people in England and Wales, 55% of whom have partial-onset seizures. [4] Two-thirds of people with active epilepsy have their epilepsy satisfactorily controlled with anti-epileptic drugs (AEDs).[4] Epilepsy is associated with a higher risk of mortality and also a number of co-morbidities, most commonly depression, neuroses, anxiety and psychoses. [1,5] More than one in five people with epilepsy have learning or intellectual disabilities.[2] Epilepsy affects many aspects of the daily lives of people, such as work, driving, life insurance and lifestyle, all of which contribute to a poorer quality of life. [6] In 2009, 69,700 people with epilepsy in England, Wales and Scotland were claiming disability living allowance, at a cost of £244million per year. [2] This review seeks to consider the evidence (clinical and cost-effectiveness) for Brivaracetam and its possible place in therapy. References: 1. NICE Clinical Guideline 137. 2015 http://www.nice.org.uk/guidance/cg137. 2. Joint Epilepsy Council (JEC) http://www.epilepsyscotland.org.uk/pdf/Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11_(3).pdf 3. Iyer A et al. Expert Opin Pharmacother. 2014; 15(11):1543–51. 4. NICE. Retigabine. Final scope. October 2010. 2010; https://www.nice.org.uk/guidance/ta232/documents/epilepsy-partial-retigabine-adjuvant-final-scope 5. Gaitatzis A et al. Epilepsia. 2004; 45(12):1613–22. 6. Kwan P et al. Expert Opin Emerg Drugs. 2007; 12(3):407–22.

Summary Key points

- Brivaracetam is a highly selective, reversible synaptic vesicle protein 2A (SV2A) ligand which displays similar selectively, but higher affinity, than levetiracetam, the other SV2A ligand available.[1, 2]
- Brivaracetam is indicated 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.
- Brivaracetam requires no up-titration to reach therapeutic dose, addressing patient needs and expectations for a simple, effective, long-term treatment.
- Brivaracetam will not supplant levetiracetam, which should be considered before Brivaracetam is initiated.
- One study has shown that brivaracetam 100mg/day does not have a clinically relevant effect on the pharmacokinetics of the combined oral contraceptive containing ethinylestradiol 30mcg and levonorgestrel 150mcg (no data is available for a dose of 50 or 200 mg/day).[2] A 400mg/day dose (not a licensed dose) increased the clearance of ethinylestradiol and levonorgestrel but there was no impact on suppression of ovulation.[1, 4]
- No dose adjustment of brivaracetam is required when co-administered with other AEDs such as carbamazepine, lamotrigine, oxcarbazepine, phenytoin, topiramate or valproic acid.[1]
- The safety and efficacy of brivaracetam has been evaluated in adults with partial-onset seizures across four phase III studies. Patients enrolled in these studies had epilepsy of a refractory nature and in one study 47.2% failed on five or more antiepileptic drugs. [5-7] Fixed brivaracetam doses were used to treat patients with uncontrolled partial-onset seizures in two studies (N01252 Ryvlin et al and N01253 Biton et al), while a flexible dosing schedule was used in N01254 (Kwan P et al) to treat patients with a broad range of epilepsies. The fourth study, N01358 (Klein P et al), was a fixed-dose efficacy and safety study in patients with uncontrolled partial-onset epilepsy. [8] Open-label extension studies are on-going.
- There are no head to head trials of brivaracetam with other anti-epileptic drugs.
- Brivaracetam is similarly priced to most other adjunct Anti-epileptic Drugs (AEDs), but it is considerably more expensive than generic levetiracetam.
- It is estimated that 15-20 patients attending Bedford Hospital will initially be initiated on brivaracetam but this number is likely to change as clinicians gain more experience with the drug and/or licence extensions are granted. If 15 patients/100,000 are treated with brivaracetam, this would equate to an annual cost of £58,144 and £118,815 to LCCG and BCCG respectively. (Likely patient numbers in Luton is currently unknown). There would be some offsetting of these costs associated with the discontinuation of other treatments.

References:
1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion.
2. Gillard M et al. Eur J Pharmacol. 2011; 664:36–44.
3. EMA. Summary of opinion (initial authorisation). Briviact (brivaracetam). EMA/CHMP/742520/2015. 2015; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003898/WC500196737.pdf.
4. Stockis A et al. J Clin Pharmacol. 2013; 53(12):1313–21.
5. Biton V et al. Epilepsia. 2014; 55(1):57–66.
6. Ryvlin P et al. Epilepsia. 2014; 55(1):47–56.
7. Kwan P et al. Epilepsia. 2014; 55(1):38–46.
8. Klein P et al. Epilepsia. 2015; doi: 10.1111/epi.13212.

Evidence level

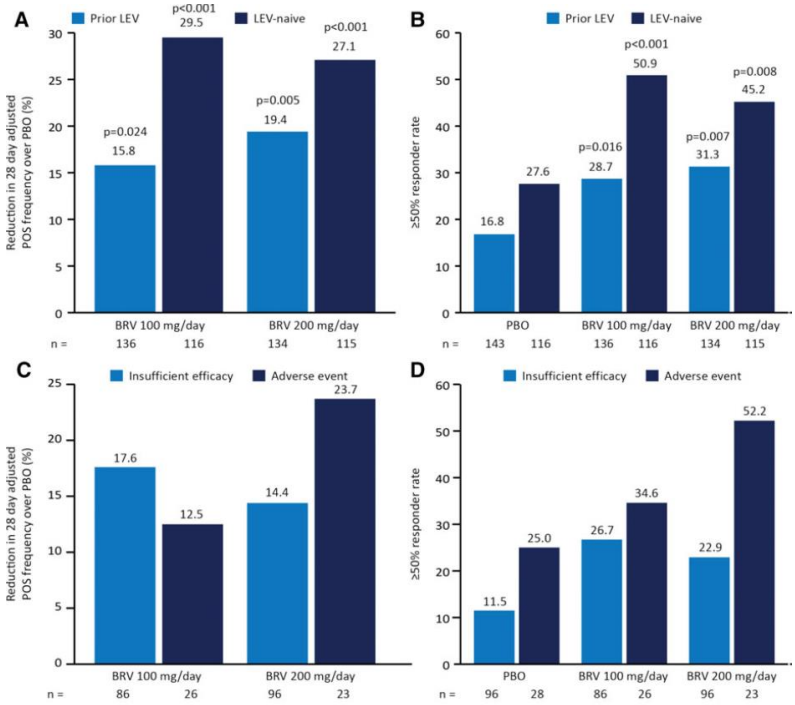
Class 1 level of evidence that adjunctive brivaracetam is effective in reducing POS frequency in adults with epilepsy and uncontrolled seizures. Ben-Menachem et al (Neurology 2016; 87:314–323).

The intervention Mechanism of action	Brivaracetam is a highly selective, reversible synaptic vesicle protein 2A (SV2A) ligand which displays similar selectively, but higher affinity, than levetiracetam, the other SV2A ligand available. [1, 2] 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. [1] References: 1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion. 2. Gillard M et al. Eur J Pharmacol. 2011; 664:36–44.
Licensed indication	Brivaracetam is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy. [1] References: 1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion.
Formulation/Available Products	Film Coated Tablets 10mg, 25mg, 50mg, 75mg, 100mg Oral solution 10mg/ml Solution for injection or infusion 10mg/ml, (infusion over 15mins) [1] References: 1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion.
Usual dosage	Treatment initiation of brivaracetam is with the therapeutic dose. The recommended therapeutic dose is 50 mg – 200 mg per day. The recommended starting dose is either 50 mg/day or 100mg/day, based on physician assessment of required seizure reduction versus potential side effects.[1] The dose should be administered in two equally divided doses, once in the morning and once in the evening. The dose may be adjusted in the dose range 50 mg/day to 200 mg/day.[1] References: 1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion.
Precautions/ Special patient groups	No dose adjustment is required in elderly patients. There is limited clinical experience in patients ≥65 years of age. No dose adjustment is needed in patients with impaired renal function. Brivaracetam is not recommended in patients with end-stage renal disease undergoing dialysis, due to lack of data. In patients with chronic liver disease, a starting dose of 50 mg/day is recommended; a maximum 150 mg/day administered in two divided doses is recommended for all stages of hepatic impairment.[1] References: 1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion.
Treatment alternatives/ place in therapy	See existing formulary guidance for information on treatment alternatives. BHT has confirmed that patients are treated in accordance with NICE Guidance (see P5). Brivaracetam is recommended as an adjunctive AED treatment for adult patients (≥16 years) with partial-onset seizures. It is an efficacious treatment that provides those who required *adjunctive antiepileptic drug therapy* with an opportunity to reduce seizure frequency.[1] In is proposed that brivaracetam is recommended as an AMBER traffic light – for specialist initiation and primary care prescriber continuation only. Brivaracetam requires no up-titration to reach therapeutic dose, and has a favourable overall tolerability profile.[1]

	Brivaracetam is not supplanting levetiracetam; the use of brivaracetam is expected to be on failure of levetiracetam for efficacy or tolerability issues. Brivaracetam is not recommended for use with concomitant levetiracetam[1] References: 1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion.
Future alternatives	None at present.
National guidance	NICE guidance recommends that the AED treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the child, young person or adult's lifestyle, and the preferences of the person, their family and/or carers as appropriate. [1] Monotherapy should be used wherever possible. Failure to control seizures completely with the first well-tolerated AED is a good predictor of drug-resistant epilepsy, defined as the continuation of seizures despite optimal monotherapy with two successive first-line AEDs, or with one monotherapy and one combination regimen. [2] NICE recommends that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. [1] NICE recommends carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to patients with partial-onset seizures if first-line treatments are ineffective or not tolerated. If adjunctive treatment is ineffective or not tolerated, then the clinician should 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. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the child, young person or adult, in terms of providing the best balance between effectiveness. [1] Brivaracetam did not have a marketing authorisation when the AEDs were reviewed by NICE. [1, 3] SIGN recommends lamotrigine as the drug of choice for partial-onset seizures. Where lamotrigine is poorly tolerated, carbamazepine or levetiracetam are reasonable alternatives.[2] Once two AEDs have failed as monotherapy, the chance of seizure freedom with further monotherapy is low. Improvement in seizure control may be obtained by combining AEDs.[2] SIGN recommends combination therapy when treatment with two first-line AEDs has failed or when improved control occurs during the process of phased substitution. The choice of adjunctive AED will depend on patient factors such as sex, reproductive potential, age, concomitant medications, pre-existing or comorbid conditions, other medical or psychiatric conditions and adverse effect profile. Once the decision has been made to use combination therapy, the patient should be established on the best combination at the optimal dose, i.e. one that produces best efficacy with fewest adverse effects. The aim should be seizure freedom on the lowest number of drugs. Where an encouraging but suboptimal effect is obtained with a particular combination, it may be worthwhile trying the addition of a small dose of a third AED. [2]

	SMC recommends initiation in patients with refractory epilepsy and that treatment should be initiated by physicians who have appropriate experience in the treatment of epilepsy. The AWMSG have restricted the use of brivaracetam to 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. Brivaracetam (Briviact®) is not recommended for use within NHS Wales outside of this subpopulation. References: 1. NICE Clinical Guideline 137. 2015 http://www.nice.org.uk/guidance/cg137. 2. SIGN. SIGN 143. May 2015. 2015; Available from: http://www.sign.ac.uk/guidelines/fulltext/143/index.html. 3. EMA. Summary of opinion (initial authorisation). Briviact (brivaracetam). EMA/CHMP/742520/2015. 2015; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003898/WC500196737.pdf. 4. Scottish Medicine Consortium – SMC No 1160/16 https://www.scottishmedicines.org.uk/SMC_Advice/Advice/1160_16_brivaracetam_Briviact/brivaracetam_Briviact 5. All Wales Medicines Strategy Group. Final Appraisal Recommendation – Advice number 2516: 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. http://www.awmsg.org/awmsgonline/app/appraisalinfo/2038
Local Guidance	Brivaracetam is already available across Scotland, Wales and Ireland as well as Royal Free, Queen Square (UCLH), St George's, Kings, Oxford, Cambridge, Hertfordshire and a wide number of other CCGs and Trusts in England.
Evidence for use	**Clinical effectiveness: Impact on patient care**: Brivaracetam requires no up-titration to reach therapeutic dose, [1] addressing patient needs and expectations for a simple, effective, long-term treatment. Ben-Menachem et al (Neurology 2016; 87:314–323). This pooled analysis was conducted to assess the efficacy and safety of adjunctive brivaracetam for the treatment of partial onset seizures (POS) at the proposed dose range (50–200 mg/day). Data were pooled from patients (aged 16–80 years) with POS uncontrolled by 1 to 2 antiepileptic drugs receiving BRV 50, 100, or 200 mg/d or placebo, without titration, in 3 phases III studies of brivaracetam. The studies had an 8-week baseline and a 12-week treatment period. Patients receiving concomitant levetiracetam were excluded from the efficacy pool. In the efficacy population (n=1,160), reduction over placebo in baseline-adjusted POS frequency/28 days was 19.5% for 50 mg/d, 24.4% for 100 mg/d and 24.0% for 200 mg/d. The 50% responder rate was 34.2% (50 mg/d), 39.5% (100 mg/d), and 37.8% (200 mg/d) vs 20.3% for placebo. Overall seizure freedom rate was 0.5% for placebo versus 4.2% for brivaracetam. Across the safety population groups (n =1,262), 90.0% to 93.9% completed the studies. [2] In the 12-week N01358 Klein et al study, the percent reduction over placebo in 28-day adjusted partial-onset seizure frequency (primary endpoint) was significantly greater with both brivaracetam 100 mg/day and 200 mg/day over placebo (22.8% with 100 mg/day, 23.2% with 200 mg/day, p<0.001 for both analyses vs. placebo). The 50% responder rate based on percent reduction in partial-onset seizure frequency from baseline to the treatment period (primary endpoint) was also significantly greater with both brivaracetam doses vs. placebo (21.6% with placebo vs. 38.9% with 100 mg/day, NNT=6 and vs. 37.8% with 200 mg/day, NNT=6, p<0.001 for both brivaracetam doses vs. placebo). A total of 412 patients had previously tried and discontinued levetiracetam (LEV) due to insufficient efficacy (278, 67.5%), AEs (77, 18.7%), other reason (31, 7.5%, or unknown reason (26, 6.3%). Efficacy was demonstrated by both co-primary outcomes in the subgroups with previous LEV exposure and in LEV-naïve patients in a post hoc statistical analysis, and appeared to be greater in the LEV-naïve population. The treatment

effect appeared to be greater in patients who previously discontinued LEV due to AEs than those who reported insufficient efficacy, although the number of patients in the discontinuation due to AEs sub-groups was small. [3]



Taken from Klein et al.

Yates et al (Epilepsy & Behaviour 52(2015) 165-168). This study evaluated nonpsychotic behavioural adverse events (BAEs) in patients receiving levetiracetam who switched to brivaracetam. The study included patients who were >16yrs of age and receiving levetiracetam 1-3g per day and experiencing BAEs. Patients had an immediate switch***** from levetiracetam to brivaracetam 200mg/day (without titration) and a 12 week treatment period. 29 patients were enrolled, 26 completed. Majority of patients who switched had a clinically meaningful reduction in BAEs. 69% of patients showed a marked or moderate improvement in BAEs. Complete abatement of primary BAEs was reported 62.1% of patients. [4]

*****_*the immediate switch from levetiracetam to brivaracetam is outside of the marketing authorisation for brivaracetam.*_

Zhu L. et al (Seizure 45 (2017) 7-16). This meta-analysis was performed to comprehensively evaluate the adverse events (AEs) significantly associated with brivaracetam (BRV) treatment in a large selection of randomized control trials (RCTs). Eight RCTs with a total of 2,505 patients were included in this study, 1178 of which were randomized with respect to brivaracetam (BRV). Serious adverse events (SAEs) were reported in all trials. The number of serious AEs was 73/1787 (4.1%) for subjects randomized to brivaracetam treatment groups and 38/718 (5.3%) for subjects randomized to placebo. There was no significant difference in serious AEs between the brivaracetam and placebo treatment groups. We found there was no significant difference in the overall withdrawal rate between the BRV and placebo. AE-related withdrawal was also not associated with BRV treatment. They then analysed AE-related withdrawal in different dosage subgroups. Regardless of increasing dose, brivaracetam was not significantly associated with an increased risk of AE-related withdrawal. This meta-analysis showed that BRV treatment was reasonably tolerated by patients and rarely caused serious AEs. [5]

Kwan et al evaluated the safety and tolerability of adjunctive brivaracetam in adults with uncontrolled epilepsy. Efficacy was assessed as a secondary objective. This

	was a phase 3, randomized, double-blind, placebo-controlled flexible dose trial in adults (16 – 70). Patients were randomized to BRV or PBO, initiated at 20 mg/day and increased, as needed, to 150 mg/day during an 8-week dose-finding period. This was followed by an 8-week stable-dose maintenance period. The treatment period comprised the dose-finding period plus the maintenance period (16 weeks). A total of 480 patients were randomized (BRV 359, PBO 121); of these, 431 had focal epilepsy and 49 had generalized epilepsy. Ninety percent BRV- and 91.7% PBO-treated patients completed the study. Similar proportions of patients (BRV 66.0%, PBO 65.3%) reported adverse events (AEs) during the treatment period. AEs led to treatment discontinuation in 6.1% and 5.0% of BRV- and PBO-treated patients, respectively. The incidence of AEs declined from the dose-finding (BRV 56.0%, PBO 55.4%) to the maintenance (BRV 36.8%, PBO 40.9%) period. The most frequent AEs during the treatment period were headache (BRV 14.2% vs. PBO 19.8%), somnolence (BRV 11.1% vs. PBO 4.1%), and dizziness (BRV 8.6% vs. PBO 5.8%). The incidence of psychiatric AEs was similar for BRV and PBO (BRV 12.3%, PBO 11.6%). In patients with focal seizures, the baseline-adjusted percent reduction in seizure frequency/week in the BRV group (n = 323) over PBO (n = 108) was 7.3% (p = 0.125) during the treatment period. The median percent reduction in baseline-adjusted seizure frequency/week was 26.9% BRV versus 18.9% PBO (p = 0.070), and the ≥50% responder rate was 30.3% BRV versus 16.7% PBO (p = 0.006). In patients with generalized seizures only, the number of seizure days/week decreased from 1.42 at baseline to 0.63 during the treatment period in BRV-treated patients (n = 36), and from 1.47 at baseline to 1.26 during the treatment period in PBO-treated patients (n = 13). The median percent reduction from baseline in generalized seizure days/week was 42.6% versus 20.7%, and the ≥50% responder rate was 44.4% versus 15.4% in BRV-treated and PBO-treated patients, respectively. [6] Adjunctive BRV given at individualized tailored doses (20–150 mg/day) was well tolerated in adults with uncontrolled epilepsy, and the results provided support for further evaluation of efficacy in reducing focal and generalized seizures.[6] References: 1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion. 2. Ben-Menachem et al (Neurology 2016;87:314–323) 3. Klein P et al. Epilepsia, 56(12): 1890-1898, 2015 4. Yates S et al. Epilepsy and Behaviour. 2015;52:165-168 5. Zhu L. et al. Seizure 45 (2017) 7-16. 6. Kwan P et al. Epilepsia 2014 ; 55(1):38-46
Safety*	**Impact on patient safety: Interactions**. Multiple medications are often administered to patients with partial-onset seizures, increasing the likelihood of drug-drug interactions and adverse events. [2-5] Interactions which raise levels of concomitant AEDs may lead toxicity, while reducing their levels may increase and worsen seizures.[2-3] Brivaracetam has a low interaction potential.[1] Brivaracetam exhibits little or no inhibition of CYP450 isoforms except for CYP2C19. No dose adjustments of the brivaracetam dose are necessary when co-administered with carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproic acid. No dose adjustments of the following AEDs are necessary when brivaracetam is used concurrently with them: carbamazepine, clobazam, clonazepam, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproic acid or zonisamide.[1] **Impact on patient safety: Formulation**: Brivaracetam is available in a range of formulations, meeting the needs of all patients, including those who are unable to swallow oral tablets. Brivaracetam is available as oral tablets, an oral solution (which is suitable for dilution in water or juice and is suitable for use with a nasogastric or gastrostomy tube) and as an intravenous injection or infusion. Brivaracetam is rapidly and completely absorbed after oral administration and the absolute bioavailability is approximately 100%. When converting from oral to

intravenous, or vice versa, the total daily dose and frequency of administration should be maintained. [1]

Impact on patient safety: Adverse events: There are long-term safety data for up to 8 years. In patients who were followed up in the open-label extension studies for up to 8 years, the safety profile was similar to that observed in the short-term, placebo-controlled studies.[1] Brivaracetam is generally well tolerated. In all controlled and uncontrolled trials in patients with epilepsy, 2,388 subjects have received brivaracetam, of whom 1,740 have been treated for ≥ 6 months,1,363 for ≥ 12 months, 923 for ≥24 months and 569 for ≥ 60 months (5 years).[1] The most frequently reported adverse reactions (>10%) with brivaracetam treatment were: somnolence (14.3%) and dizziness (11.0%). They were usually mild to moderate in intensity. Somnolence and fatigue (8.2%) were reported at a higher incidence with increasing dose. The types of adverse reactions reported during the overall treatment period were similar to those reported for the first 7 days of treatment.[1] Discontinuation rates due to adverse reactions were 3.5%, 3.4% and 4.0% for patients randomised to brivaracetam 50 mg/day, 100 mg/day and 200 mg/day respectively, and 1.7 % for patients randomised to placebo. The adverse reactions most frequently resulting in discontinuation of brivaracetam therapy were dizziness (0.8 %) and convulsion (0.8%).[1]

References:
1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion.
2. Schmidt D et al. Br Med J [Internet]. 2014;348:doi:10.1136/bmj.g254. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.g254
3. Panayiotopoulos C. Chapter 4. http://www.ncbi.nlm.nih.gov/books/NBK2607/.
4. Ahmad BS et al. Neurology. 2012; 79(2):145–51.
5. Johannessen SI et al. Curr Neuropharmacol. 2010; 8(3):254–67.

Costs
Tariff status
Activity costs

Drug & Dosage	30 day cost/per patient	Annual Cost per patient
Brivaracetam[1]	£129.64 (50mg bd-100mg bd)	£1,555.68
Eslicarbazepine [8, 9]	£136.00 (800mg od)	£1,850.40
Lacosamide (Vimpat) [3, 5]	£144.16 (200mg bd)	£1,729.92
Lamotrigine (Lamictal) [2,3]	£117.35 (200mg bd)	£1,408.20
Levetiracetam (Keppra) [3,4]	£156.84 (1,500mg bd)	£1,882.08
Levetiracteam (Generic)	£7.99 (1,500mg bd)	£95.88
Oxcarbazepine [6, 3]	£109.67 (1,200mg bd)	£1,316.04
Perampanel [3, 7]	£140.00 (4mg od -12mg od)	£1,680.00

N.B. Doses are for general comparison and do not imply therapeutic equivalence

References:
1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion.
2. GlaxoSmithKline UK. Summary of Product Characteristics. Lamictal. July 2015. Available from: www.medicines.org.uk.
3. Haymarket Medical Media. MIMS: Central nervous system. Epilepsy. December 2015. Available from: www.mims.co.uk. Date accessed December 2015
4. UCB Pharma Limited. Summary of Product Characteristics. Keppra... August 2015. Available from: www.medicines.org.uk. Date accessed December 2015
5. UCB Pharma Limited. Vimpat. October 2014. Available from: www.medicines.org.uk. Date accessed December 2015
6. Novartis Pharmaceuticals UK Ltd. Summary of Product Characteristics. Trileptal. September 2014. Available from: www.medicines.org.uk. Date accessed December 2015
7. Eisai Ltd. Summary of Product Characteristics. Fycompa. June 2015. Available from: www.medicines.org.uk. Date accessed December 2015
8. NICE bnf. https://bnf.nice.org.uk/medicinal-forms/eslicarbazepine-acetate.html
9. BIAL. Summary of Product Characteristics. Zebinix 200mg and 800mg tablets. May 2017. Available from: www.medicines.org.uk. Date accessed June 2017

Cost effectiveness (if available)

Brivaracetam costs £129.64 for 4 weeks of treatment, for a dose of 50 mg/day or 100 mg/day (recommended starting dose based on physician assessment of

	required seizure reduction vs. potential side effects) through to 200 mg/day (maximum recommended dose).[1] The drug acquisition costs of brivaracetam are consistent with those of other recent market entrants treating the same population. For example, the daily cost for brivaracetam tablets for 28 days treatment is flat priced for at £129.64 (50mg BD / 75mg BD / 100mg BD). Brivaracetam is similarly priced to the other adjunct AEDs, the generic levetiracetam is considerably cheaper. Brivaracetam would be used in patients who are uncontrolled on/intolerant to levetiracetam. References: 1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion.
Potential number of patients in Bedfordshire and Luton **Impact per 100,000 population** **Affordability considerations**	15-20 is the estimated number of patients attending Bedford Hospital who may be initiated on Brivaracetam; this number may change in accordance with licence extensions later and also as the clinical team become more au-fait with the drug. Likely patient numbers in Luton were unknown. In a population of 100,000, an estimated 924 people over the age of 16 years will have epilepsy and of these, 55% (n=508) will have a diagnosis of partial seizures with or without secondary generalisation. [2, 3] Of these, 30% (n=152) will require adjunctive AED therapy. [4] Brivaracetam may be appropriate for a proportion of these. If 10% of these patients (n=15 per 100,000) are treated with brivaracetam, the drug acquisition cost per year (at a dose of 100 mg daily) is £25,279.80. This would equate to an annual cost of £58,144 and £118,815 to LCCG and BCCG respectively. There would be some offsetting of these costs associated with the discontinuation of other treatments. When considering appropriate treatments for patients with epilepsy we always seek monotherapy and seizure freedom. However, for those patients who progress to refractory epilepsy (failed two monotherapy options) then combination therapy is necessary. The choice of drug combination is tailored to the patient and their needs as well as comorbidities. Generally patients will be on one adjunctive therapy so it's about choosing what we think will work best for each patient. There are no additional costs because the patient will be receiving one of the drugs. References: 1. UCB Pharma Ltd. Summary of Product Characteristics Briviact tablets, oral solution and solution for injection/infusion. 2. JEC. Joint Epilepsy Council of the UK and Ireland. Epilepsy prevalence, incidence and other statistics. 2011 ;(September). Available from: http://www.epilepsyscotland.org.uk/pdf/Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11_ (3).pdf. Date accessed December 2015 3. NICE. Retigabine for the adjunctive treatment of partial onset seizures in epilepsy. Final scope. October 2010. 2010; Available from: https://www.nice.org.uk/guidance/ta232/documents/epilepsy-partial-retigabine-adjuvant-final-scope2. Date accessed: March 2015 4. NICE. Costing statement: Retigabine for the adjunctive treatment of partial onset seizures in epilepsy. July 2011. 2011. Available from: http//www.nice.org.uk/guidance/ta232/resources. Date accessed December 2015.

Decisions from other bodies	Scottish Medicine Consortium, AWMSG (All Wales Medicines Strategy Group), NCPE Ireland (and HSE Ireland) – have approved brivaracetam for use. (see National Guidance section above)
Comments sought from –	Consultant Neurologists at Bedford Hospital NHST Trust, the Luton & Dunstable NHS Trust and Milton Keynes NHS Trust.
Evidence strengths and limitations	The safety and efficacy of brivaracetam has been evaluated across various studies including Phase II and Phase III trials, open label studies and meta analyses, in adults with partial-onset seizures. (please refer to references) 5,558 patient year's exposure. 3,673 patients have taken brivaracetam; some patients have been monitored for up to 8 years. With 768 patients the Klein et al study is one of the largest interventional studies conducted to date in patients with epilepsy. As with all new AEDs there are no head to head studies available. There is currently little information to guide clinical decision-making regarding optimal combination of AEDs based on mechanism of action. The concept of "rational polytherapy" is an area for future study.

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

**Consult Summary of Prescribing Characteristics for full prescribing detail.*

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Appendix 1- Search Strategy

NICE
British National Formulary
Electronic Medicines Compendium
NHS Evidence
Medline

Treatment assessed (September 2017): Brivaracetam for Epilepsy

JPC Recommendation

- Brivaracetam is supported for use within its marketing authorisation (as an 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) in patients who have refractory epilepsy and are intolerant to levetiracetam (prescribed as the generic preparation) or have co-morbidities/receiving interacting medication which would preclude its use.
- Treatment must be initiated by the specialist neurology service and may be continued by GPs.

1) Clinical Effectiveness

• The safety and efficacy of brivaracetam has been evaluated in adults with partial-onset seizures across four phase III studies. Patients enrolled in these studies had epilepsy of a refractory nature and in one study 47.2% failed on five or more antiepileptic drugs. 5-7 Fixed brivaracetam doses were used to treat patients with uncontrolled partial-onset seizures in two studies (N01252 Ryvlin et al and N01253 Biton et al), while a flexible dosing schedule was used in N01254 (Kwan P et al) to treat patients with a broad range of epilepsies. The fourth study, N01358 (Klein P et al), was a fixed-dose efficacy and safety study in patients with uncontrolled partial-onset epilepsy. 8 Open-label extension studies are on-going.

• There are no head to head trials of brivaracetam with other anti-epileptic drugs.

2) Cost Effectiveness

• Brivaracetam is similarly priced to most other adjunct Anti-epileptic Drugs (AEDs), but it is considerably more expensive than generic levetiracetam.

• It is estimated that 15-20 patients attending Bedford Hospital will initially be initiated on brivaracetam but this number is likely to change as clinicians gain more experience with the drug and/or licence extensions are granted. (Likely patient numbers in Luton is currently unknown). If 15 patients/100,000 are treated with brivaracetam, this would equate to an annual cost of £58,144 and £118,815 to LCCG and BCCG respectively. There would be some offsetting of these costs associated with the discontinuation of other treatments.

3) Equity

No issues identified.

4) Needs of the community

15-20 is the estimated number of patients attending Bedford Hospital who may be initiated on Brivaracetam; this number may change in accordance

with licence extensions later and also as the clinical team become more au-fait with the drug.

In a population of 100,000, an estimated 924 people over the age of 16 years will have epilepsy and of these, 55% (n=508) will have a diagnosis of partial seizures with or without secondary generalisation. 2, 3 Of these, 30% (n=152) will require adjunctive AED therapy.

Brivaracetam may be appropriate for a proportion of these. If 10% of these patients this would equate to 15 patients/100,000 population.

5) Need for healthcare (incorporates patient choice and exceptional need)

Alternative Anti-epileptic drugs are available.

6) Policy drivers

NICE

7) Disinvestment

There may be some offsetting of costs if brivaracetam replaces alternative anti-epileptic drugs.

The JPC agreed the following sections within the PCT Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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