East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Prescribing Clinical Network

Medicine and proposed indication	**Brivaracetam** Indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in epileptic patients from 16 years of age.
Requested by	Dr. Graham Warner, Royal Surrey County Hospital Dr Jeff Kimber , Surrey and Sussex Healthcare Trust

SUMMARY

Clinical Effectiveness

This medicine has a high level of evidence for efficacy as an adjunctive treatment of partial-onset seizures when compared to placebo[3], but a very low level of evidence for efficacy when compared to its analogue, levetiracetam.

Two meta-analyses have assessed the efficacy and safety data from several phase II and III trials of brivaracetam. All trials were randomised, double-blind and placebo-controlled. Participants were adults with a history of focal onset seizures despite use of at least one antiepileptic drug (AED). Brivaracetam was used at doses ranging from 5 mg to 150 mg daily, and the trials lasted between 7 and 16 weeks. There were a total of 1,590 participants across all trials although numbers exposed to any one dose were rather lower, ranging from n = 100 (100 mg) to n = 305 (50 mg). The primary outcomes were the responder rate (defined as the proportion of patients with a reduction in seizure frequency of ≥50%) and rate of seizure freedom. Patients taking any dose of brivaracetam daily were significantly more likely to respond to treatment than the placebo group (risk ratio [RR] 1.80, 95% CI 1.43 to 2.26, p< 0.0001) When separated by dose, this effect remained for patients taking 20-100 mg brivaracetam daily. One of the included trials allowed dose titration up to a maximum of 150 mg, but did not report results by dose. One meta-analysis included these data in the 150 mg subgroup and found a significant difference compared to placebo, while the other excluded them entirely and did not find any difference between brivaracetam 150 mg and placebo. There was no difference between brivaracetam 5 mg and placebo in any analysis[3]

Complete seizure freedom was more common with brivaracetam 50 mg than placebo, but there was no significant difference in this outcome for any other dose in the meta-analyses. One phase III trial not included in these analyses found that seizure freedom was also more common with brivaracetam 100 mg daily (p=0.003) and 200 mg daily (p=0.02) than placebo. The additional trial was a 12 week double blind randomised comparison (n = 768) of brivaracetam 100 mg and 200 mg with placebo. Seizure frequency was reduced in both treatment groups by approximately 23% (p<0.001), and treatment response was more common in the 100 mg group (38.9%) and the 200 mg group (37.8%) than with placebo (21.6%, p (p<0.001) for both comparisons). A significant proportion of participants (n = 412) had previously tried treatment with levetiracetam but discontinued due to lack of efficacy (n = 278), adverse effects (AEs, n = 77) or other reasons. A post-hoc analysis found brivaracetam to be less effective in this subgroup than in the trial population as a whole.

<u>Strengths and limitations of the evidence</u> The published meta-analyses included trials of good quality, with low risk of bias. However, the longest trial only lasted 16 weeks whereas therapy for epilepsy is likely to be long term. There are no trials against active comparators. Level of evidence*

1+ Meta-analyses with a low risk of bias.

Three randomised controlled trials in people with focal seizures showed brivaracetam was associated with a significantly greater response to treatment than placebo, but there are no trials that directly compare brivaracetam with other adjunctive treatments for epilepsy and evaluated for seizure size and frequency[5].

Subgroup analyses of studies N01252 and N01253 showed no benefit for brivaracetam in patients taking concomitant levetiracetam[6]

Study N01358 excluded patients taking concomitant levetiracetam; however, a post hoc analysis found BRV was effective for both levetiracetam -naive patients and those with prior levetiracetam exposure[7] (High risk of false results with Post Hoc analysis[8])

Most trials used a fixed-dose design although one study did allow titration from a starting dose of 20 mg. A total of 52% of patients reached the maximum of 150 mg daily and a further 25% reached 100 mg daily. Results were reported for the brivaracetam group as a whole, with no breakdown according to dose. Only one trial tested the maximum licensed dose of 200 mg daily, and efficacy appeared similar to the 100 mg daily group for the primary outcomes of seizure frequency and ≥50% responder rate. The meta-analyses found no apparent increase in response rate with doses >50 mg/day so there is little evidence that increasing dose leads to better seizure control. However, the number of people treated with any single dose was relatively small, so any small changes in effectiveness may not have been detected. [3]

Brivaracetam tablets cost £1,685 per person per year. This is considerably more expensive than the first choice drugs for adjunctive therapy (see chart below) including its' comparator drug levetiracetam at a cost of £71 per person per year, but comparable to newer second line choices such as eslicarbazepine, lacosamide or zonisamide.

There are potentially 980 patients across the population across the PCN collaborative who have focal onset seizures which are refractory to monotherapy[10]. A proportion may switch treatment from existing second-line therapies to brivaracetam because they have not provided an adequate response or have not been tolerated. The proportion of people who may switch treatment is unknown. Feedback from providers suggests approximately 1.5-2 patients per 100,000 population.

<u>Chemistry:</u>

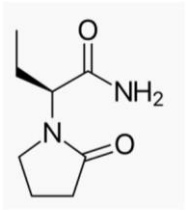
Brivaracetam has an additional N-propyl group to levetiracetam. This increases lipophilicity of the brivaracetam (both drugs are still very water soluble, and highly bioavailable). This makes the brivaracetam more potent than levetiracetam as is reflected in the lower licensed dose – brivaracetam, up to 200mg per day, levetiracetam, up to 3000mg per day.

Note that increased potency does not mean that a drug is more effective: Efficacy is what produces clinical benefit.

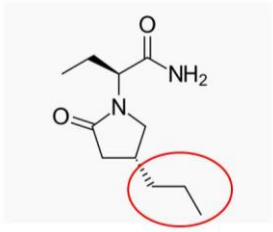
This review seeks to evaluate whether there is any evidence of benefit of brivaracetam, when compared to levetiracetam with regards to efficacy and with regards to incidence of adverse effects in order to make an informed decision about its' place in therapy.

Chemical Structure

Levetiracetam



Brivaracetam



Adverse effects:

UCB Pharma highlights differences in SPC which indicate that aggression, anger and mood swings have been reported less often, so far, for brivaracetam than for levetiracetam[9]. There are no head-to-head trials.

Safety

When the data for all doses were pooled, there was no difference in the overall rate of treatment-emergent adverse events or serious adverse events when compared to placebo[3]

Patient factors

Around 20% to 30% of newly diagnosed patients will have drug resistant epilepsy. The International League against Epilepsy (ILAE) defines drug-resistant epilepsy as failure of adequate trials of two tolerated and appropriately chosen AED schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area in patients with treatment resistant/refractory epilepsy[6].

Cost implications

At £1685 per annum, the cost of brivaracetam is commensurate with other second line choices such as eslicarbazepine, lacosamide or zonisomide, but much more expensive than levetiracetam at £71 per annum. It is being marketed specifically for use as a third line treatment.
As described in the review, the likelihood of brivaracetam being effective for patients who did not respond or did not tolerate levetriacetam has not been demonstrated, but which is hoped for from the theoretical benefits. The cost implication of trialling this treatment will depend entirely on appropriate review and decision to discontinue treatment for those patients for whom the treatment has not benefitted.

Relevent guidance / reviews

Regional Drug & Therapeutic Centre New Drug Evaluation No. 149 May 2016,
http://rdtc.nhs.uk/sites/default/files/publications/nde_149_brivaracetam.pdf
Scottish Medicines Consortium
https://www.scottishmedicines.org.uk/SMC_Advice/Advice/1160_16_brivaracetam_Briviact/brivaracetam_Briviact
All Wales Medicine Strategy Group October 2016
http://www.awmsg.org/awmsgonline/app/appraisalinfo/2038

Likely place in therapy relative to current treatments

NICE guidance recommends that monotherapy should be used wherever possible.

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. 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.

Brivaracetam did not have a marketing authorisation when the AEDs were reviewed by NICE. It is being marketed to have the same place in therapy as the tertiary treatment options

Recommendation to PCN

From the decision making criteria to support the colour classification by the prescribing clinical network, the lack of evidence of benefit compared with standard, combined with the fact that it is less cost effective than standard therapy would place this as a **BLACK – Not recommended** classification.

The members of the PCN should consider whether the very high clinical need of these patients, together with a small, theoretical possibility that it may reduce the number and severity of seizures merits the approval of this treatment despite the lack of direct evidence, with appropriate restrictions to ensure careful use in the appropriate place in therapy.

It has also been approved in neighbouring Formularies for restricted use, and therefore the members of the PCN should consider how to manage patients referred to those centres.

Most centres have approved very limited use of this product. Many have restricted to tertiary centres only.

If the PCN agrees that brivaracetam should be available, the members should consider and decide on the following restrictions:

- Should its' use be restricted to tertiary centres?
- Is it reasonable to expect GPs to prescribe this drug once the patient has shown efficacy and is dose stabilised?
- If prescribable in primary care, how long should the patients remain under specialist care to evaluate efficacy (3months? 6 months?)
- What traffic light classification would be appropriate?
    - **BLUE – Specialist input WITHOUT formal shared care agreement** – generally approval would meet this criteria with the exception that agreement from GPs to continue treatment is not required and therefore it will be difficult to ensure appropriate place in therapy
- Should it be prescribed after ***all*** the first line treatments have been considered From *NICE*?
    - *First-line treatment - Carbamazepine or lamotrigine*
    - *Levetiracetam, oxcarbazepine or sodium valproate if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these five AEDs. Be aware of the teratogenic and developmental risks of sodium*
    - *Consider adjunctive treatment if a second well-tolerated AED is ineffective (see recommendations - carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate*
    - *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.*
    - Should brivaracetam be added to this final list?

- Should brivaracetam not be prescribed unless levetiracetam has already been tried and failed.

Medicine details	
Name and brand name	Brivaracetam (Briviact®)
Licensed indication, formulation and usual dosage	Briviact® 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. • Tablets 10mg, 25mg, 50mg, 75mg and 100mg • Injection, 10mg per ml • Oral solution, 10mg per ml 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.[1]
Summary of mechanism of action, and relevetiracetamant pharmacokinetics	Please refer to product Summary of Product Characteristics at https://www.medicines.org.uk/
Important drug interactions	Please refer to product Summary of Product Characteristics at https://www.medicines.org.uk/
Monitoring requirements	Renal impairment Brivaracetam is not recommended in end-stage renal disease patients undergoing dialysis due to lack of data. Hepatic impairment Exposure to brivaracetam was increased in patients with chronic liver disease. A 50 mg/day starting dose should be considered. A maximum daily dose of 150 mg administered in 2 divided doses is recommended for all stages of hepatic impairement[2] Please refer to product Summary of Product Characteristics at https://www.medicines.org.uk/
Prescribing considerations	Please refer to product Summary of Product Characteristics at https://www.medicines.org.uk/
Other considerations	Summary of restrictions: AWMSG: Brivaracetam (Briviact®) is recommended as an option for restricted use within NHS Wales. 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, 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.

Potential patient group (if appropriate to include)	
Brief description of disease	
Potential patient numbers per 100,000	10
Outcomes required	This is very difficult to quantify and therefore poses a very difficult aspect when assessing efficacy: Trials were very short (12 weeks) and there is a 'honeymoon effect' for

	many epileptic patients. There is also a wide range of seizure frequency: From several per day which can be easy to measure, to very sporadic, which is much harder to measure but, which could result in a loss of the permission to drive if that loss of control is lost.

Summary of current treatment pathway

NICE CG137 recommends monotherapy for focal seizures wherever possible, with carbamazepine and lamotrigine considered the first-line options Adjunctive therapy is advised if monotherapy with two well-tolerated AEDs is not effective. The first line options for adjunctive treatment include carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate. Eslicarbazepine, retigabine, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide may be considered if a first-line choice is ineffective or not tolerated.
However, these are only recommended by NICE following advice from a tertiary specialist.

Evidence review

Please refer to :
Regional Drug & Therapeutic Centre New Drug Evaluation No. 149 May 2016
All Wales Medicine Strategy Group October 2016
Midlands Therapeutics Review and Advisory Committee July 2016

Equity / Stakeholder views (if relevant)

Decisions of local Trusts DTCs and neighbouring APCs	**North Central London Joint Formulary Committee** – April 2016. Decision: Not approved **Frimley Health NHS Foundation Trust DTC** – accessed 19th October-2016 Decision: Amber (with restrictions) **Crawley CCG and Horsham and Mid Sussex Joint Formulary** Decision: Non Formulary – Not yet considered by prescribing committees GPs should NOT be requested to prescribe by secondary care. **South East London Area Prescribing Committee – July 2016** Amber – Specialist (consultant neurologist) initiation and supply. GPs may be asked to take on prescribing after at least 6 months. Brivaracetam is accepted for use within South East London as an adjunctive third line treatment option for the management of partial-onset seizures with or without secondary generalisation in adults. Brivaracetam may be considered if there is: Failure of one or more first line drugs (carbamazepine, lamotrigine or levetiracetam) AND Failure of one or more 2nd line drugs (topiramate, pregabalin, lacosamide, zonisamide or perampanel)
Recommendations from national / regional decision making groups	**Regional Drugs & Therapeutics Committee (Newcastle) – May-2016** Decision: Brivaracetam should be reserved for initiation by tertiary specialists following treatment failure with existing first- and second-line adjunctive drugs. **All Wales Medicines Strategy Group – October 2016** Decision: Brivaracetam (Briviact®) is recommended as an option for restricted use within NHS Wales. 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, 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. **Midlands Therapeutics Review and Advisory Committee – July 2016** MTRAC opinion was that the clinical diagnosis, initial management and stabilisation of patients with refractor epilepsy are specialist functions. Once a

	person is stabilised on brivaracetam, it may be appropriate for primary care prescribers to continue maintenance treatment with the guidance and support of a shared care agreement. **Greater Manchester Medicines Management Group – July 2016** The group does not recommend the routine use of brivaracetam. It may however be considered for refractory patients in whom first line and adjunctive AED options as outlined in NICE CG 137: appendix E: (Pharmacological treatments) have failed. i.e. as an option in the third column titled 'Other AEDs that may be considered on referral to tertiary care' and for initiation by specialist epileptologists only. The evidence for safety and efficacy for brivaracetam is limited by the short clinical trials and lack of any comparisons with current treatment options. It is unclear what extra benefit this drug will add however clinical experts consulted considered that there is unmet need in this therapeutic area in patients with treatment resistant/refractory epilepsy. According to set criteria was deemed to be a medium priority for funding. Use of brivaracetam as outlined will be audited in 12 months' time. In Germany IQWIG has also evaluated the drug. The evaluation report is in the German, but the essence of the evaluation carried out by IQWIG was that they found no evidence of an additional benefit of Brivaracetam over the appropriate comparator therapy: https://maestrodatabase.com/blog/brivaracetam-in-epilepsy-additional-benefits-not-seen/ The full IQWIG German report can be accessed here: https://www.iqwig.de/de/presse/pressemitteilungen/pressemitteilungen/brivaracetam-bei-epilepsie-zusatznutzen-nicht-belegt.7334.html?&et_cid=4&et_lid=%25208
Stakeholder views	Ashford and St. Peter's Foundation Trust: From: Jan Coebergh Sent: 22 December 2016 09:48 To: Carolyn Adamson; Adrian Fowle; David Barnes; Khaled Abdel-Aziz Cc: cjoanes@nhs.net Subject: RE: Evidence review Dear Carina, (and cc to others) We see it as a potentially useful adjunct that we will rarely use in all likelihood (like perampanel; I have one patient on it (of many 100s of my epilepsy patients). It is however important that we can use it; it is not dangerous or too expensive and if longer term it has less psychiatric side effects than levatiracetam there are situations where rapid loading as in/outpatient (more rapid than lamotrigine/carbamazepine) will be helpful. KR Dr Jan Coebergh --- Royal Surrey County Hospital **From:** WARNER, Graham (ROYAL SURREY COUNTY HOSPITAL NHS

FOUNDATION TRUST)
Sent: 19 December 2016 18:28
To: JOANES, Carina (NHS SURREY DOWNS CCG)
Subject: Re: Evidence review

GOOD WORK-THX

If the PCN agrees that brivaracetam should be available, the members should consider and decide on the following restrictions:

- Should its' use be restricted to tertiary centres? *BUT THIS IGNORES LOCAL EXPERT KNOWLEDGE & EXPERIENCE & SIGNIFICANTLY ADDS TO CARE COST, 5% MORE WITHIN M25, & DOUBTLESS LOTS MORE TESTS….IF DGH NEUROLOGIST TRIES IT & IT FAILS LIKELY COME OFF THE AED WITHIN 1Y SO COST OF SPECIALIST UNIT ADD CONSIDERABLY IF DECISION ON THIS OR ANY KNEW AED REQUIRED. DILUTES THE RESOURCE/VALUE OF THE TERTIARY CENTRE. IF THE DRUG WORKS THEN VALUE FOR MONEY AVOIDING FITS & ADDITIONAL CARE!*

- Is it reasonable to expect GPs to prescribe this drug once the patient has shown efficacy and is dose stabilised? *IF GP DOESN'T PRESCRIBE CLOGS UP NEUROLOGY CLINICS IF DRUG, SO AGAIN UNDERMINES RESOURCE & ADD COST TO CARE.*

- If prescribable in primary care, how long should the patients remain under specialist care to evaluate efficacy (3months? 6 months?) *SIMILAR ISSUES TO LAST BULLET POINT, DEPENDS ON WHAT ADDITIONAL RESOURCE/SUPPORT THE IS FOR THIS LTC!*

- Should it be prescribed after all the first line treatments have been considered? *CLINICAL EXPERT DECISION….REASONABLE TO TRY 3-4 BEFORE THIS. MOST LIKELY WILL BE 7-8 DOWN THE LINE OF LATER!*

- Should brivaracetam not be prescribed unless levetiracetam has already been tried and failed. *LEV WILL HAVE BEEN TRIED ANYWAY!...POTENTIAL USE WHEN LEV WORKS BUT A SIDE EFFECT WE WANT TO ADDRESS/AVOID*

Graham

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NHS Secretary: anne.cunningham@nhs.net
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fax: 01483 406749

Frimley Health Foundation Trust

From: GALTREY, Clare (ST GEORGE'S UNIVERSITY HOSPITALS NHS FOUNDATION TRUST)
Sent: 23 January 2017 14:25
To: JOANES, Carina (NHS SURREY DOWNS CCG)
Cc: Jan Arevalo - Epilepsy Specialist Nurse; Jeremy Stern - Consultant - Neurologist
Subject: Re: Response to Evidence review for Brivaracetam

I am sorry - it is Queens Square - the National Hospital for Neurology and Neurosurgery

Clare

From: JOANES, Carina (NHS SURREY DOWNS CCG)
Sent: 23 January 2017 14:21
To: GALTREY, Clare (ST GEORGE'S UNIVERSITY HOSPITALS NHS FOUNDATION TRUST)
Cc: Jan Arevalo - Epilepsy Specialist Nurse; Jeremy Stern - Consultant - Neurologist
Subject: RE: Response to Evidence review for Brivaracetam

Thank you, I will convey this information to the PCN. Could you please advise me what the letters 'QS' stand for?

Best regards
Carina

From: GALTREY, Clare (ST GEORGE'S UNIVERSITY HOSPITALS NHS FOUNDATION TRUST)
Sent: 23 January 2017 14:05
To: JOANES, Carina (NHS SURREY DOWNS CCG)
Cc: Jan Arevalo - Epilepsy Specialist Nurse; Jeremy Stern - Consultant - Neurologist
Subject: Re: Response to Evidence review for Brivaracetam

Dear Carina,

Thank you for your response. I have reviewed the 9 patients who have been initiated on Brivaracetam here at Frimley Park with Jan Arevalo our epilepsy specialist nurse.

All are patients who have refractory epilepsy and who have tried all available alternatives, with the exception of 1 who has significant behavioural/ mood disturbances and who my predecessor felt the mode of action of potential benefit but was not prepared to risk behavioural deterioration with Levetiracetam. All of them have received regular review and follow up. 4 of them have been weaned off due to adverse effects or no perceived benefit within the first 3 months.

In the patients who continue, 1 is under the joint care of QS and her response is still being evaluated, 4 have had benefit in either seizure frequency or intensity.

I hope this experience demonstrates that brivaracetam will be used in very small numbers of patient with refractory epilepsy and we will continuously assess for efficiency and stopped if not effective. It is reasonable that brivaracetam will not be prescribed unless levetiracetam has been tried and optimised.

Clare

Dr Clare Galtrey
Frimely Park Hospital

From: JOANES, Carina (NHS SURREY DOWNS CCG)
Sent: 16 January 2017 15:21
To: GALTREY, Clare (ST GEORGE'S UNIVERSITY HOSPITALS NHS FOUNDATION TRUST)
Cc: JOHNS, Clare (NHS SURREY DOWNS CCG)
Subject: RE: Response to Evidence review for Brivaracetam

Dear Clare, thank you for your e-mail.

I will include your comments to the presentation at PCN, however, as you would imagine, the PCN has many clinicians who are very well versed on evidence based medicine, and will be looking very closely at the evidence. If they are asked to approve this treatment on the same merits of other treatments they are asked to approve, the answer is likelyto be no.

In order to maximise the credibility within the PCN, I think it is important to recognise the sparcity of evidence, but argue that these patients have a very high need, and describe the steps you will take to ensure that this expensive medicine will be managed to maximum benefit –

If you could provide the following information/ assurances to the PCN, I am sure that there is a better chance for it to be approved:

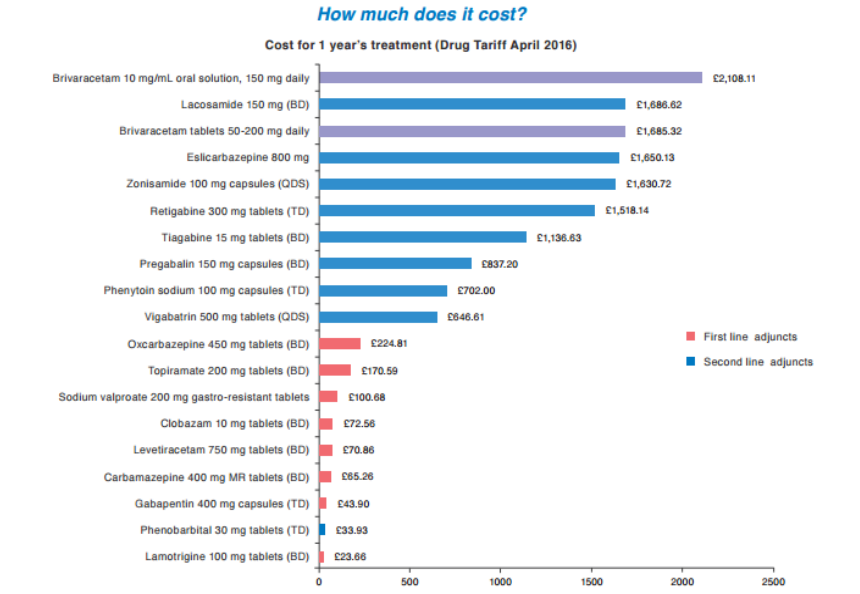
If you look carefully at the evidence, there is really very little to justify the use of brivaracetam over levetriacetam (The Class 1 evidence is

	when compared to placebo which is as expected as brivaracetam is almost identical to levetiracetam). · Brivaracetam will not be prescribed unless levetiracetam has been tried and optimised (i.e. appropriate dose initiation and dose titration) as well as most of the other first line treatments as recommended in the NICE guidance CG137 (after carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate have already been tried). · When you initiate, when will you assess for efficacy taking into consideration the 'honeymoon effect' often associated with new treatments for intractable disease, and how will you ensure that the treatment is discontinued if not more effective than previous treatments. From the marketing material there is reference to fewer reported adverse events, but this needs to be seen in the context that there have been many fewer patients on this treatment, and for a much shorter duration and therefore, as reports are absolute and not relative, so this information needs to be taken with great caution. I am happy to discuss further, and, of course you are welcome to attend the meeting (1st February 2017, 14.30 – 17.00. The timing of this item can be allocated at the most convenient time for you) Best regards Carina **From:** GALTREY, Clare (ST GEORGE'S UNIVERSITY HOSPITALS NHS FOUNDATION TRUST) **Sent:** 11 January 2017 21:30 **To:** JOANES, Carina (NHS SURREY DOWNS CCG) **Cc:** Jeremy Stern - Consultant - Neurologist **Subject:** Fw: Response to Evidence review for Brivaracetam I would be grateful if the following statement could be submitted when considering the formulary application for Brivarcetam. I have recently been appointed to replace Dr O'Dwyer as the Epilepsy Led Neurologist at Frimley Park Hospital Declaration: I have no conflicts of interest. If you need any further infromation or of the declaration of interests needs to be submitted on a specific form please let me know and I am very happy to complete it. Best wishes Clare There is class 1 evidence that brivaracetam is effective for adjunctive

	treatment of partial-onset seizures when compared to placebo (1). It has a favourable safety, tolerability and pharmacokinetics profile making it a promising antiepileptic choice for patients with uncontrolled partial-onset seizures. There have not been head to head trials of brivaracetam and levetiracetam, a meta-analysis and indirect comparison of the two drugs that involved 13 trials suggested that brivaracetam might not be superior levetiracetam (2). However it is important to note clinical trials are not usually powered to show superiority of one AED over another but to demonstrate equivalence or lack of inferiority. It is unlikely that double-blind, randomized controlled trials of brivaracetam and levetiracetam will be conducted in the foreseeable future. Given their similar mechanisms of action, their combination will probably not be useful. There is evidence of better tolerability of brivaracetam. One small, open-label, prospective study suggested that, in patients who switched from levetiracetam to brivaracetam because of behavioural adverse events, quality of life improved and there was no loss of seizure control (3). A systematic review of 17 RCTs of new generation AEDs suggests a better tolerability of brivaracetam than eslicarbazepine, and perampanel, at the highest effective recommended dose with similar efficacy (4). Brivaracetam provides an important option for a small group of patients with uncontrolled partial-onset seizures for whom a new drug for seizure control is always welcome. It has a good efficacy, safety and tolerability profile and is a viable alternative for patients who do not achieve seizure control or who suffer intolerable effects with other treatments.It is now on the formulary at Frimley Health and a small number of patients have improved seizure control with fewer side effects. Patients in Surrey and Sussex would also benefit for its inclusion on the forumulary for adjuctive treatment after first line drugs have failed to control seizures. The level of evidence and cost is similar to drugs currently used in this context such as lacosamide,zonisamide and perampanel. 1. Lattanzi S, Gagnetti C, Foschi N, Provinciali L, Silvestrini M. Brivaracetam add-on for refractory focal epilepsy: a systematic review and meta-analysis. Neurology. 2016;86:1344-1352 2. Zhang L, Li S, Li H, Zou X. Levetiracetam vs. brivaracetam for adults with refractory focal seizures: a meta-analysis and indirect comparison. Seizure. 2016;39:28-33. 3. Yates SL, Fakhoury T, Liang W, Eckhardt K, Borghs S, D'Souza J.;> An open-label, prospective, exploratory study of patients with epilepsy switching from levetiracetam to brivaracetam. Epilepsy Behav.;> 2015;52:165-168. 4. Brigo et al Efficacy and tolerability of brivaracetam compared to lacosamide, eslicarbazepine acetate, and perampanel as adjunctive treatments in uncontrolled focal epilepsy: Results of an indirect comparison meta-analysis of RCTs. Seizure. 2016;42:29-37.

	Dr Clare Galtrey Specialist Trainee in Neurology Frimley Park Hospital
CCG priorities	

Health economic considerations

Cost per year per patient	
Alternative treatments cost per patient per year	See above
Other financial considerations (if relent)	The longest trial only lasted 16 weeks whereas therapy for epilepsy is likely to be long term[3]. If considering the model where patients are initiated treatment, monitor for response, and only continue treatment in those patients with a clinically important response, there is no evidence to suggest timelines for evaluation and discontinuation.
Health economic data (if available)	Please refer to Regional Drug & Therapeutic Centre New Drug Evaluation No. 149 May 2016[3] NICE suggests that in 2011 epilepsy had a prevalence of approximately 0.8-1%, equating to around 322,000 adult people in England. NICE estimates that around 52% of patients (167,000) have focal onset seizures, and of these around 30% (50,000) have focal seizures which are refractory to monotherapy which is equivalent to **72 patients per 100,000 population.** FPFT estimated around 100 patients would be eligible for treatment. Brivaracetam tablets cost £1,685 per person per year. This is considerably more expensive than the first choice drugs for adjunctive therapy (see chart below) but comparable to newer second line choices such as eslicarbazepine, lacosamide or zonisamide

References

1. Summary of Product Characteristics, www.medicines.org.uk Accessed 23 June 2016
2. North Central London Joint Formulary Committee – 28 April 2016, accessed 23 June 2016
3. Regional Drug & Therapeutic Centre New Drug Evaluation No. 149 May 2016
4. All Wales Medicines Strategy Group October 2016, accessed 10/10/2016
5. Midlands Therapeutics Review and Advisory Committee – July 2016, accessed 10/10/2016

6. Scottish Medicines Consortium, June 2016, accesed 12/10/2016, https://www.scottishmedicines.org.uk/files/advice/brivaracetam_Briviact_FINAL_June_2016_for_website.pdf
7. Ben-Menachem, E., Mameniškienė, R., Quarato, P. P., Klein, P., Gamage, J., Schiemann, J., Johnson, M. E., Whitesides, J., McDonough, B. and Eckhardt, K. (2016) 'Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies', Neurology, 87 (3): 314–323, http://www.neurology.org/content/early/2016/06/22/WNL.0000000000002864.full.pdf
8. *9.6.6 interpretation of subgroup analyses and meta-regressions* (no date) available at http://handbook.cochrane.org/chapter_9/9_6_6_interpretation_of_subgroup_analyses_and_meta_regressions.htm, accessed 13 October 2016
9. Response with regards to questions on clinical efficacy and safety, UCB pharma, Sent: 15/09/2016
10. NICE. TA232 Retigabine for the adjunctive treatment of partial onset seizures in epilepsy. Costing statement. July 2011. http://www.nice.org.uk/guidance/ta232/resources/ costing-statement-423502957.

Prepared by:

Date: 19th October 2016

Reviewed by: Name, designation and organisation

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
1	26/09/2016	G. Randall		
2	19/12/2016	C Joanes		
3	25/01/2017	C Joanes		Following colleague feedback, added evidence from 'Regional Drug & Therapeutic Centre New Drug Evaluation No. 149 May 2016' to ensure the evidence is in the same document as the review. Economic data also updated in the Summary section of this review.

https://www.nice.org.uk/guidance/cg137/chapter/1-Guidance#pharmacological-treatment

[20] In this recommendation, 'partial seizures' has been replaced with 'focal seizures' to reflect a change in terminology since the original guideline was published in 2004.

1.9.3 Pharmacological treatment of focal seizures

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

1.9.3.1Offer carbamazepine or lamotrigine as first-line treatment to children, young people and adults with newly diagnosed focal seizures. **[new 2012]**

1.9.3.2Levetiracetam is not cost effective at June 2011 unit costs[13]. 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. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)[14]. **[new 2012]**

1.9.3.3Consider adjunctive treatment if a second well-tolerated AED is ineffective (see recommendations 1.9.3.1 and 1.9.3.2). **[new 2012]**

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

1.9.3.4Offer carbamazepine, clobazam[15], gabapentin[15], lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with focal seizures if first-line treatments (see recommendations 1.9.3.1 and 1.9.3.2) are ineffective or not tolerated. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)[14]. **[new 2012]**

1.9.3.5If adjunctive treatment (see recommendation 1.9.3.4) 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[15], lacosamide, phenobarbital, phenytoin, pregabalin[15], tiagabine, vigabatrin and zonisamide[15]. Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields. **[new 2012]**

East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Comments on Evidence review for Prescribing Clinical Network

Here is a draft email to send out the papers:

Please find attached a draft copy of an evidence review for _____ which has been produced for consideration at the Prescribing Clinical Network (PCN) on _____.

Please include any comments you have to any questions asked as well as any additional references you feel may need to be included in the review to us by _____, using the template below. If there are any other colleagues that you feel we need to engage with please also let us know their names and where/how they can be contacted.

Please note that for anyone commenting on the document, Declarations of Interest will be required to be submitted for each person or your comments will not be taken into consideration.

Any comments and additional information received will then be incorporated into the review and circulated to the PCN member for consideration at the meeting.

It is important that we receive your input into this evidence review and we value your comments. Decisions made at the PCN will affect the treatment of your patients. Please note that if you do not use this opportunity to give your feedback on this review, it will be assumed that you do not disagree with its contents.

The PCN values clinician input and welcomes their attendance at the meeting and if you like to attend to support the review you are most welcome, however, due to limited meeting room capacity, we would recommend the nomination of one clinician to represent the group, please contact me if you like to attend.

Thank you for your time and for assisting the PCN in making cost-effective, evidence-based recommendations for the treatment of our patients.

We look forward to hearing from you. If you have any questions, please let us know.

Yours sincerely,

(Name and include telephone number)

Comments on Evidence review for Prescribing Clinical Network

Medicine and proposed indication	
Prepared by	Name, designation and organisation
Comments on evidence review	
Additional evidence and references for consideration	Include any additional evidence and references you would like to submit for inclusion in the evidence review
Specific clinical questions	Specific questions arising from review
Other colleagues who should be contacted	Include name, designation and contact details of any other colleagues who should be consulted about this evidence