CLINICAL PRIORITIES ADVISORY GROUP
06 and 07 November 2018

Agenda Item No	04.3
National Programme	Women and Children's Programme of Care
Clinical Reference Group	Paediatric Neurosciences
URN	170093P

Title
Everolimus for refractory partial-onset seizures associated with tuberous sclerosis complex (age 2 years and above)

Actions Requested	1. Support the policy proposition
	2. Recommend the relative priority

Proposition
Routinely commissioned Tuberous Sclerosis Complex is a genetic condition that can lead to non-cancerous growths developing in the brain, eye, heart, kidney, skin and lungs. Seizures are one of the most common neurological features of TSC. The rate of psychiatric problems in people with TSC is high and the four main disorders reported are depression, anxiety, attention deficit disorder and aggressive/disruptive behaviours. In infants and children with TSC, seizures are closely related to development. Specifically, intellectual disability is associated with a history of infantile spasm and refractory seizures. The rate of learning disability in people with epilepsy is high, especially in children who develop epilepsy early in life. The policy proposition is recommending that everolimus should be used as an add on therapy and made available to patients aged 2 years and over who have TSC related seizures that have not responded adequately to treatment with at least two different Anti-Epileptic Drugs, where epilepsy surgery has failed or is unsuitable and where vagus nerve stimulation has failed or is not considered appropriate.

Clinical panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes / Head of Mental Health Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Operational Delivery Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition -		
No	*Metric*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver /	

	supporting independence	
10.	Safety	All adverse events. The largest study (Franz, 2018) studied 361 patients up to 2 years indicates that the most frequent treatment-related adverse effects were stomatitis (33.5%), mouth ulceration (26.0%), diarrhoea (10.5%), aphthous ulcer (10.2%), and pyrexia (10.2%). The occurrence of adverse effects did not increase over time. Adverse events led to treatment discontinuation in 47 patients (13%), primarily due to pneumonia (1.7%) and stomatitis (1.4%). There were 4 deaths, 2 were thought to be treatment-related deaths (pneumonia and septic shock; both in children). The results from the studies suggest that most patients treated with everolimus may experience an adverse event, but that adverse events did not increase over time.
11.	Delivery of intervention	

Other health metrics determined by the evidence review		
No	Metric	Summary from evidence review
1	Response rate of 50% reduction in seizures	Response rate of 50% reduction in seizures is the percentage of patients who had at least half the number of seizures they were having at the start of the study. The largest study (French, 2016) with 366 patients reported a response rate of 50% reduction in seizures in 40% of patients treated with high dose everolimus and 28% of patients treated with low dose everolimus, compared to 15% of patients receiving anti-epileptic drugs (AEDs) only (the placebo group) after 12 weeks follow-up. The longest-term evidence from the largest extension trial available (Franz et al., in 2018) included 361 patients from the original trial who were all given everolimus. The trial reported a 50% reduction in seizure frequency in 31% of patients at week 18, 46.6% at 1 year, and 57.7% at 2 years of treatment with everolimus. For patients that were able to continue treatment with everolimus (in other words, patients who did not discontinue treatment for any reason), median seizure frequency reduced by 31.7% at week 18, 46.7% at 1 year, and 56.9% at 2 years treatment. The median number of additional seizure-free days (per 28-day period) was 6.15 days at 2 years of everolimus exposure. The greatest benefit was reportedly observed in patients initially randomised to high exposure everolimus, leading the study authors to report that the benefit of everolimus is dependent on length of treatment

		(longer treatment durations corresponded with better outcomes) and exposure to everolimus (higher exposure corresponded with better outcomes). Ninety-five patients (26.3%) discontinued everolimus before the end of 2 years. The authors did a sensitivity analysis assuming that patients who discontinued everolimus for any reason had done so because their seizures had not responded to treatment (regardless of the reported reason). Even using this assumption, everolimus was found to reduce seizure frequency by at least 50% in 30.2% (95%CI, 25.5-35.2; N=361) of people at week 18, 38.8% (95%CI, 33.7-44.1; N=358) at 1 year, and 41% (95%CI, 34.6-47.7; N=229) at 2 years, which suggests sustained benefit over time. The results from French (2016) and Franz (in 2018) suggest that 30% of patients treated with everolimus can expect a 50% reduction in seizure frequency from baseline at week 12 after starting treatment. The results also suggest that the benefit of treatment can increase over time. The greatest benefit was reported in patients initially randomised to high dose everolimus.). It should be noted that the patients included in the study had a higher seizure frequency rate than expected in patients in England and just under half had tried 6 or more AEDs previously.
2	Median % reduction in seizures	Median percentage reduction in seizures is a measure of the reduction in seizure frequency relative to baseline seizure frequency at the start of the study. The largest study (French, 2016) with 366 patients reported a median 40% and 29% reduction in seizures in the high and low dose everolimus groups, respectively at 12 weeks follow-up. In the AED only (placebo) group, there was a median 15% reduction in seizures in patients. The longest-term evidence from the largest extension trial (Franz, 2018) reported a median 31.7% reduction in seizure frequency at week 18, a median 46.7% reduction at 1 year, and a median 56.9% reduction at 2 years. The results from the French (2016) and Franz (2018) suggest that patients treated with everolimus can expect a 29% reduction in seizure frequency at week 12. The results also suggest that the benefit of treatment can increase over time. The greatest benefit was reported in patients initially randomised to high dose everolimus.

		It should be noted that the patients included in the study had a higher seizure frequency rate than expected in patients in England and just under half had tried 6 or more AEDs previously.
3	Median number of additional seizure free days per 28 days	The median number of additional seizure free days per 28 days a measure of the additional number of days without any countable seizures in a 28 day period. The largest and longest study (Franz, 2018) reported that the median number of seizure-free days (per 28-day period) increased from 2.5 days at week 18, to 4.32 at 1 year, and 6.15 days at 2 years of everolimus treatment. Data from French 2017 are captured in this analysis. The results from the Franz study (2018) suggest that patients treated with everolimus can expect 2.5 seizure-free days at week 18 with everolimus. The results also suggest that the benefit of treatment can increase over time. The greatest benefit was reported in patients initially randomised to high dose everolimus, leading the study authors to report that the benefit of everolimus is dependent on length of treatment (longer treatment durations corresponded with better outcomes) and exposure to everolimus (higher exposure corresponded with better outcomes). It should be noted that the patients included in the study had a higher seizure frequency rate compared to the expected seizure frequency rate for patients with refractory TSC-related seizures in England and just under half had tried 6 or more AEDs previously.
4	Patients remaining seizure free	Patients remaining seizure free is a measure of the number of patients in the trial who had no countable seizures during the trial. The largest study (French, 2016) with 366 patients reported that 6 out of 117 (5%) patients in the low dose everolimus group and 5 out of 130 (4%) patients in the high dose everolimus group had no countable seizures compared to 1 out of 119 (0.8%) patients in the AEDs only (placebo) group at 12 weeks follow up. The longest-term evidence from the largest extension trial (Franz, 2018) included 361 patients from the original trial who were all given everolimus. The trial reported that 15 out of 275 (5%) patients at receiving everolimus were seizure-free over the previous 6 months at year 1 of the study and 13 out of 117 (11%) patients were seizure-free over the previous 6 months at year 2.

		The results from the French and Franz studies suggest that 4 out of 100 patients treated with everolimus can expect seizure freedom at week 18 of everolimus treatment and that the benefit of treatment with everolimus can increase over time. The greatest benefit was reported in patients who were remained in the study, leading the study authors to report that the benefit of everolimus is dependent on length of treatment (longer treatment durations corresponded with better outcomes). It should be noted that the patients included in the study had a higher seizure frequency rate compared to the expected seizure frequency rate for patients with refractory TSC-related seizures in England and just under half had tried 6 or more AEDs previously.
5	Quality of life	Quality of life is a measure of a patient's quality of life. It is usually based on a questionnaire which is completed by the patient or parent/carer. Like other outcomes, it is measured at baseline and then again during and at the end of the study. The largest study (French, 2016) with 366 patients reported that there was no difference in quality of life measures. A study with 20 patients (Krueger, 2013) reported a benefit in Quality of Life Childhood Epilepsy (QOLCE) questionnaire, which was driven by improvements in attention, behaviour, and social interaction domains. No improvement in quality of life was reported was during the extension study (Krueger, 2016). The results from the studies suggest that patients treated with everolimus may not see a consistent benefit in quality of life measures. The results from Krueger should be interpreted with caution as they are based on a small single arm study. It means that it did not randomise patients or compare the treatment with any other standard treatment. It should also be noted that the French (2016) study had difficulties in collecting the quality of life data, due to many of the patients enrolled having cognitive impairments which prevented the measurement of quality of life using the questionnaires available.
6	Changes to concomitant AED medication	Changes to concomitant AED medication means a measurement of changes to the amount and type of AEDs taken by patients in the studies in addition to everolimus or placebo. The largest study with 361 patients was the extension of the main trial (Franz, 2018). In the extension study, patients together with their treating clinician were allowed to make

		changes to their AED medication. This study reported that the proportion of AEDs patients were receiving at baseline remained the same over 2 years and 47% of patients received the same AED regimen for 1 year or longer during the extension study. The results from the extension study suggest patients being treated with everolimus can expect no change in their AED usage over time. This also suggests that there is less of a need to try a different AED medication as efficacy is maintained with the current AED with everolimus as add on treatment. It should be noted that the just under half of patients in the Franz study had tried 6 or more AEDs previously.
7	Patient behaviour	Patient behaviour means changes in patient behaviour over time including changes positive (or social) and negative (or antisocial) behaviours. The largest study (Krueger, 2013) with 20 patients reported mixed results indicating an improvement (reduction) in negative behaviour, but no significant improvement in positive behaviours. The results of the extension study (Krueger, 2016) suggested no difference in patient behaviour over 48 months. The results from the studies suggest that patients treated with everolimus may not see a clear improvement in behaviour. The results from Krueger should be interpreted with caution as they are based on a small single arm study. It means that it did not randomise patients or compare the treatment with any other standard treatment. It should also be noted that the French (2016) study had intended on collecting the patient behaviour data, but was unable to do so due to many of the patients enrolled having cognitive impairments which prevented the measurement of patient behaviour using the questionnaires available.
8	Discontinuation rates	Discontinuation rates means the number of patients who stopped using everolimus for any reason during the trial. The largest study (Franz, 2018) which studied 361 patients up to 2 years indicated that 105/ 361 patients (29%) discontinued everolimus during up to the data cut off of September 2016. The main reasons for discontinuation were adverse events (12.7%), withdrawal of consent (7.2%), and because it was not reducing the frequency or severity of seizures anymore (5.8%)

		The results from the studies suggest that some patients treated with everolimus may stop taking it due to side effects or because it is no longer reducing the frequency or severity of their seizures. The results should be interpreted with caution as this was a trial setting, and the number of patients stopping treatment clinical practice could vary.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This policy proposition recommends everolimus for patients with refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above) which is within its licensed indication. Everolimus is excluded to tariff.

Considerations from review by National Programme of Care
The proposal received the full support of the Women & Childrens PoC Board on the 24 May 2018 and continues to support the proposition.