CPAG Summary Report for Clinical Panel – URN1700 Everolimus for refractory partial-onset seizures associated with tuberous sclerosis complex

The Benefits of the Proposition –			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [A]	All Adverse events The largest study (Franz, in press) studied 361 patients up to 2 years. The unpublished results from Franz et al. have been taken into account by the policy working group based on a confidential draft of the article which was provided by the company. This will be published in the near future and will be available at the time a commissioning policy is considered for routine commissioning. 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	Not measured	

Other health outcome measures determined by the evidence review			
No	Outcome measure	Grade of evidence	Summary from evidence review
1.	Response rate of 50% reduction in seizures	Grade A	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 AEDs only (the placebo group) after 12 weeks follow-up. The longest-term evidence from the largest extension trial available (Franz et al., in press) 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 (these preceding data will be included in Franz et al., but have already been presented in a poster and therefore are not considered academic-in-confidence). The unpublished results from Franz et al. have been taken into account by the policy working group based on a confidential draft of the article which was provided by the company. This will be published in the near future and will be available at the time a commissioning policy is considered for routine commissioning. The results from French (2016) and Franz (in press) 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	Grade A	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, in press) 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 (in press) 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	Grade A	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 unpublished results from Franz et al. have been taken into account by the policy working group based on a confidential draft of the article which was provided by the company. This will be published in the near future and will be available at the time a commissioning policy is considered for routine commissioning. 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	Grade A	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, in press) included 361 patients from the original trial who were all given everolimus. The unpublished results from Franz et al. have been taken into account by the policy working group based on a confidential draft of the article which was provided by the company. This will be published in the near future and will be available at the time a commissioning policy is considered for

			routine commissioning. 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	Grade A	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	Grade A	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, in press). In the extension study, patients together with their treating clinician were allowed to make changes to their AED medication. The unpublished results from Franz et al. have been taken into account by the policy working group based on a confidential draft of the article which was provided by the company. This will be published in the near future and will be available at the time a commissioning policy is considered for routine commissioning. 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	Grade B	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	Grade B	Discontinuation rates means the number of patients who stopped using everolimus for any reason during the trial. The largest study (Franz, in press) which studied 361 patients up to 2 years. The unpublished results from Franz et al. have been taken into account by the policy working group based on a confidential draft of the article which was provided by the company. This will be published in the near future and will be available at the time a commissioning policy is considered for routine commissioning. 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.