

Clinical Commissioning Policy: Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above)

NHS England Reference: 170053P



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Specialised Commissioning
Commissioning Strategy

Publications Gateway Reference:**07603****Document Purpose**

Policy

Document Name

Clinical Commissioning Policy: Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above)

Author

Specialised Commissioning Team

Publication Date

29 June 2018

Target Audience

CCG Clinical Leaders, Care Trust CEs, Foundation Trust CEs , Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Directors of Commissioning Operations, Directors of Finance, NHS Trust CEs

Additional Circulation List**Description**

Not for routine commissioning

Cross Reference**Superseded Docs**
(if applicable)**Action Required****Timing / Deadlines**
(if applicable)**Contact Details for further information**

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Document Status

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Clinical Commissioning Policy: Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above)

First published: June 2018

**Prepared by National Institute for Health and Care Excellence (NICE)
Commissioning Support Programme for NHS England Specialised Services**

Published by NHS England, in electronic format only.

CONTENTS

1	Introduction	8
2	Definitions	9
3	Aims and Objectives	11
4	Epidemiology and Needs Assessment.....	11
5	Evidence Base	13
6	Documents which have informed this Policy	17
7	Date of Review.....	17
	References.....	18

Policy Statement

NHS England will not routinely commission everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above).

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to suspend or rescind policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About seizures associated with tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a genetic condition. It 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 and occur in approximately 84% of people.

It is estimated that around 5.6 in 100,000 people are born with the condition. In many cases the diagnosis is made during childhood, when symptoms become apparent.

The impact of TSC varies considerably. Some people are mildly affected and may not even know they have TSC, while others are much more affected.

About current treatments

For people with TSC-related seizures, anti-seizure medication (known as anti-epileptic drugs or AEDs) is the standard treatment. For an AED to be considered appropriate it must have previously been shown to be effective for the patient's epilepsy and seizure type.

For people whose TSC-related seizures have not adequately responded to treatment with at least 2 different AEDs given at therapeutic doses, other treatment options are available. This includes:

- the additional use of 1 or more AED added on to their currently prescribed AED or the use of a different AED which has not been previously prescribed; and
- the following treatments:
 - a ketogenic diet (a diet low in carbohydrates) usually for infants and young children (because it is difficult for adolescents and adults to remain on a strict diet); and/or
 - vagus nerve stimulation (a device which stops seizures by sending regular, mild pulses of electrical energy to the brain and is implanted

under the skin in the chest and connected to the vagus nerve, which is the main nerve that connects the brain to the heart, lungs, upper digestive tract, and other organs of the chest and abdomen); and/or

- surgical resection (surgical resection may not be suitable for everyone with TSC-related seizures that have not adequately responded to treatment with at least 2 different AEDs given at therapeutic doses. This is because many patients with TSC-related seizures will not have a single type of seizure which is clearly related to one location in the brain that can safely be removed. In addition, some patients choose not to undergo surgery. However, children with TSC-related refractory seizures should be assessed for surgical resection in accordance with NHS England's Children's Epilepsy Surgery Service Specification, November 2016 [Ref: E09/S/e]). Adults should be assessed under a specialised epilepsy surgery multidisciplinary team (MDT).

About the new treatment

Everolimus is a drug that targets a pathway that regulates cell growth and multiplication. In patients with TSC, the mammalian target of rapamycin (mTOR) is over-activated, leading to uncontrolled growth of brain cells. This can result in tumours as well as elevated excitability of the brain cells which can lead to seizures. Everolimus dispersible tablets have a marketing authorisation in England as add-on treatment for patients aged 2 years and older with TSC-related seizures that have not adequately responded to treatment with at least 2 different AEDs given at therapeutic doses.

What we have decided

NHS England has carefully reviewed the evidence available for everolimus as an add on treatment for people aged 2 years and older who have TSC-related seizures that have not adequately responded to treatment with at least 2 different AEDs given at therapeutic doses, and where epilepsy surgery has failed or is unsuitable and where VNS has failed or is not considered appropriate as the next treatment option by the patient, or their carer in discussion with the treating clinician. NHS England recognises the published evidence identifies that at present, there is sufficient

evidence to commission this treatment. However, following the relative prioritisation process undertaken in May 2018 for funding in 2018/19, NHS England has concluded that, balanced against other relative priorities that were also considered during the process, this intervention will not be funded at this time within the resources available. The policy will however be reconsidered in the next prioritisation round, scheduled for November 2018.

1 Introduction

TSC is a condition that people are born with that often leads to non-cancerous growths developing in the brain, eye, heart, kidney, skin and lungs. TSC tumours of the brain can cause seizures. Seizures are one of the most common symptoms of TSC and occur in approximately 84% of people ([Kingswood et al, TOSCA data, 2017](#)). It is estimated that there are 1359 people with refractory seizures associated with TSC in England.

Seizures are considered to be refractory when 2 different anti-epileptic drugs (AEDs) given at therapeutic doses have failed to control a person's seizures (also known as uncontrolled or intractable).

The most common treatment used in UK clinical practice is AEDs. According to NICE clinical guideline 137, 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 and their family and/or carers as appropriate. In children, other treatment options for refractory seizures include a ketogenic diet, vagus nerve stimulation (VNS) or surgical resection. In adults, other treatments for refractory seizures include VNS and less commonly a ketogenic diet (due to the difficulty of remaining on the strict diet indefinitely) or surgical resection.

Everolimus) is a disease modifying drug in TSC that targets the mTOR pathway. It works by blocking the over-activation of mTOR (a major cell growth and proliferation controller), which is thought to be the cause of seizures in people with TSC. The dispersible tablets are licensed by the European Medicines Agency as 'adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures

(focal onset seizures), with or without secondary generalisation (focal to bilateral tonic clonic seizures), are associated with tuberous sclerosis complex' (EMA/H/C/002311 -II/0044 2017). They are administered orally. Dosage depends on body surface area and age.

Treatment may last for many years, since everolimus is not curative. The Summary of Product Characteristics (SPC) for everolimus dispersible tablets state that 'treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs'.

2 Definitions

Adjunctive: 'add on'

Everolimus: a drug similar to rapamycin, which acts by inhibiting mTOR which is overactivated in people with TSC.

Focal onset seizures: In 2017, the International League Against Epilepsy (ILAE) approved a new way of classifying seizures that reflects recent advances in our understanding of the brain and seizures. In this 2017 Classification, 'focal onset seizures' replaces 'partial onset seizures' and refer to those that start in an area or network on one side of the brain. Focal onset seizures may start with the person aware or with impaired awareness. It may then spread to involve both sides of the brain and the person would be unaware during the seizure. The majority of seizures in people with TSC are focal onset seizures (Fisher, et al., 2017).

Focal onset seizures evolving to bilateral tonic clonic: in the 2017 ILAE Classification, the term 'focal to bilateral tonic clonic seizure' replaces 'partial onset seizure with secondary generalisation'. This occurs when the seizure has spread to both sides of the brain, leading to loss of awareness and bilateral convulsive movements. (Fisher, et al., 2017). As the majority of TSC seizures have a focal origin, 'focal onset seizures' will be used throughout this document to refer to focal onset seizures with or without evolution to bilateral tonic clonic seizures.

Ketogenic diet: a high-fat, adequate-protein, low-carbohydrate diet. The diet forces the body to burn fats rather than carbohydrates. If there are few carbohydrates in the diet, the liver convert fats into ketone bodies which are an energy source. An elevated level of these ketone bodies in the blood can lead to a reduction in the frequency of epileptic seizures.

Mammalian target of rapamycin (mTOR): a pathway that regulates cell growth and multiplication.

Partial onset seizures: the term previously used for 'focal onset seizures'.

Quality of Life Childhood Epilepsy (QOLCE) questionnaire: a questionnaire for children with epilepsy which is completed by patients' parents to enable an assessment on the quality of life in children aged 4-18 years

Rapamycin: also known as sirolimus is a drug which mainly suppresses the immune system.

Refractory seizures: this means that 2 different anti-epileptic drugs (AEDs) given at therapeutic doses have failed to control a person's seizures.

Status epilepticus: when a seizure lasts longer than 5 minutes or when seizures occur close together without recovery in between.

SUDEP: sudden unexpected death in epilepsy.

Surgical resection: surgery to remove tumours which may be causing seizures.

Therapeutic dose: a dose that is just enough to provide the intended effect without causing undesired effects.

Tonic clonic seizure: this type of seizure (also called a convulsion) is what most people think of when they hear the word 'seizure'. This type of seizure is a combination of tonic and clonic seizures where tonic means stiffening, and clonic means rhythmical jerking (Fisher, et al., 2017).

Tuberous Sclerosis Complex (TSC): a genetic disorder characterised by the development of multiple benign tumours, mainly in the brain, kidney, liver, skin, heart and lungs.

Vagus nerve stimulation: sometimes referred to as a "pacemaker for the brain", this is a device which is implanted under the skin in the chest and connected to the vagus nerve (the main nerve that connects the brain to the heart, lungs, upper digestive tract, and other organs of the chest and abdomen). It stops seizures by sending regular, mild pulses of electrical energy to the brain.

3 Aims and Objectives

This policy considers everolimus as add-on treatment of refractory focal seizures associated with TSC in people aged 2 years and older.

The objectives are to ensure evidence based commissioning for patients with refractory focal onset seizures associated with TSC in people aged 2 years and older.

4 Epidemiology and Needs Assessment

The estimated prevalence of the condition in the UK is 5.6 per 100,000 (Hallet et al, 2011)*.

Based on this, it is estimated there are 3126 patients in England with TSC. However, this is likely to be an underestimation of the true prevalence, because prevalence is increasing with better identification of less severe cases.

Approximately 84% of people with TSC have epilepsy and the majority of these people have focal onset seizures (equating to 2626 people).

The proportion of patients with TSC-related refractory epilepsy varies depending on the evidence source between 36% (Kingswood et al., 2017) and 63% (Chu-Shore et al., 2010). Based on this, the number of people with TSC-related refractory epilepsy in England is 1359. See table below.

Estimates	Data source	Number of people
Population in England in mid-2016	Office for National Statistics	55,268,100
5.6 in 100,000 with TSC	* Public Health England and Policy Working Group Clinical Lead	3126
Epilepsy is in 84% of TSC patients	(Kingswood et al, TOSCA data, 2017) – from company submission	2626
Refractory to treatment - 36% to 63%	(Kingswood et al, TOSCA data, 2017) – from company submission (Chu-Shore et al. 2010)	1359

TSC is primarily diagnosed in children and young adults (aged 20 or younger), although it may present in patients as late as age 40.

In infants and children with TSC, seizures are closely related to development. Specifically, intellectual disability is associated with a history of infantile spasm (seizures which occur in infants) and refractory seizures (Wang and Fallah, 2014). The rate of learning disability in people with epilepsy population is high, especially in children who develop epilepsy early in life (NICE CG137). Early management of seizures is important in preventing and reducing the cognitive, neurological and psychiatric consequences from refractory seizures (Bombadieri, 2010). Generalised tonic–clonic seizures was the strongest predictor of decline across a wide range of cognitive functions (Thompson et al., 2005). Long term intellectual development is thought to be improved if seizure treatment starts as soon as a child is diagnosed with epilepsy and when that treatment provides a prompt response (NICE CG137). Sudden unexpected death in epilepsy (SUDEP) is an important cause of mortality in people with TSC-related refractory epilepsy (Amin et al., 2016). Analysis of epilepsy studies have identified frequent convulsive seizures (3 or more in a year) as a major risk factor for SUDEP (Hesdorffer et al., 2011; Ryvlin et al., 2013) and several studies indicate that unsupervised night-time seizures significantly contribute to SUDEP risk (Lamberts et al., 2012). The aim of treatment, therefore, is to stop or reduce the number and frequency of seizures in patients with TSC as much as possible to limit the cognitive and neuropsychiatric consequences of refractory epilepsy and also ultimately to reduce the risk of SUDEP. These benefits have not

been demonstrated with regard to treatment with everolimus, but are based on extrapolating the associations between seizure frequency and cognitive and neuropsychiatric outcomes.

The rate of psychiatric problems in people with TSC is high. The four main disorders reported are depression, anxiety, attention deficit disorder and aggressive/disruptive behaviours (Muzykewicz, et al., 2007). Treatment with certain AEDs is known to increase the degree of cognitive and behavioural disorders in people with TSC-related seizures (French and Staley, 2012). In making a care plan for a child, young person or adult with learning disabilities and epilepsy, particular attention should be paid to the possibility of these adverse cognitive and behavioural effects of AED therapy (NICE CG137).

5 Evidence Base

Seven studies were included in the clinical evidence review. Of those, two studies formed the main evidence for this policy proposal: the randomised controlled trial (RCT- EXIST-3, French. 2016) that formed the basis for the marketing authorisation for this indication and a follow-up extension to that study (Franz, in press).

French was a double-blind, randomised, multi-centre trial evaluating the efficacy and safety of everolimus in patients age 2 (1 in Europe, however no one under age 2 was recruited to the study) to 65 who have refractory TSC -seizures. At the time the patients joined the study, they were being treated with a stable regimen of 1 to 3 AEDs. To remain in the study, patients could not change the type or amount of AED medication they had been taking during the 8 week lead-in period before the study began. The reason for this was to ensure that the responses to treatment observed during the trial would mainly be due to the treatment effect of everolimus or placebo. The trial was conducted according to published protocols, reported clearly and included 366 patients. A majority (>80%) of patients included in the trial were aged under 18 years of age. Patients received a high exposure of everolimus, a low exposure of everolimus or placebo.

For the first 6 weeks of the study, the dose of everolimus was slowly increased to the therapeutic dose (as is reflected in the marketing authorisation for everolimus). That

therapeutic dose was then maintained for the following 12 weeks. The study inclusion criteria required that people have a clinically definitive diagnosis of TSC and refractory epilepsy (in the trial, the inclusion criterion relating to refractory epilepsy was 'a prior history of failure to control partial-onset seizures despite having been treated with two or more sequential regimens of single or combined antiepileptic drugs' [See <https://clinicaltrials.gov/ct2/show/NCT01713946?term=EXIST-3&rank=1> accessed October 2017]. For the purposes of the study, only patients who had more than 16 seizures (with no continuous 21-day seizures-free period) during the baseline period of the study were included. The patients recruited to the study had a baseline seizure rate of 34.5 to 42 seizures in a 28 day period and half of the included patients had been treated with 6 or more AEDs.

Is everolimus clinically effective in reducing the frequency of seizures in patients with refractory focal onset seizures associated with confirmed TSC in people aged 2 years and older compared with no intervention?

The evidence from 1 RCT and its extension study indicates that everolimus as add on treatment is effective at reducing the frequency of seizures compared to treatment with AEDs only. In the trial, 28.2% of patients receiving the lower dose of everolimus and 40.0% of patients receiving the higher dose of everolimus experienced at least a 50% reduction in the number of seizures they had experienced prior to starting treatment, compared to 15.1% of patients receiving placebo. A reduction in seizure frequency of 25% or greater was seen in 52.1% (95% CI 42.7–61.5) of patients in the low exposure everolimus group, and in 70.0% (95% CI 61.3–77.7) of the patients in the high-exposure everolimus group, compared to 37.8% (95% CI 29.1–47.2) in the placebo group. Across each treatment group, there was a 29.3% and 39.6% median reduction in seizure frequency at 12 weeks in the lower dose and higher dose of everolimus compared with baseline, and a 14.9% median reduction in seizure frequency compared with baseline in the group receiving placebo.

The trial population included the population covered by the marketing authorisation with respect to seizure burden and prior AED use at baseline, however, the median values for seizure burden and AED use at baseline were higher than would be expected in NHS clinical practice (median seizure frequency per 28 days at baseline

was 37.8 seizures [1 to 874] and just under half of the population had tried 6 or more AEDs at baseline).

In Franz (in press), the follow up study to French, 361 of the patients from the EXIST-3 study were followed for up to 2 years. Patients who had originally received everolimus during the main trial remained on everolimus, and patients that originally received placebo were switched to everolimus. Patients were allowed to change AED or alter their AED dose during the follow up period. However, 47% of patients remained for a year or more on stable doses of the AEDs they were using throughout the study. For patients that were able to continue treatment with everolimus (in other words, patients who did not discontinue treatment for any reason), their median seizure frequency reduced by 31.7% at week 18, 46.7% at 1 year, and 56.9% at 2 years treatment. A total of 57.7% of 163 patients achieved a 50% or greater reduction in seizure frequency at 2 years. 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. 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.

Behaviour and quality of life

The French study investigators had intended to report the effect of everolimus on patient behaviour using the Vineland Adaptive Behaviour Scale Survey. However, investigators were unable to perform the survey at baseline for many of the patients due to the severity of the patient's disability.

Evidence from the other studies included in the clinical evidence review for everolimus, suggested that behaviour improved during everolimus treatment. The Krueger 2013 study was a single arm study which included 20 patients which

assessed the benefit of everolimus on seizure control in patients with TSC-related refractory epilepsy using the Nisonger Child Behaviour Rating Form. The study showed there was a statistically significant reduction in negative domain behaviour (which include conduct problems, anxiety, hyperactivity, self-injury, self-isolation and oversensitivity). There was also an improvement in positive domain behaviour (which includes compliance and social adaptiveness) although this was not statistically significant. There was a statistically significant increase in the overall Quality of Life Childhood Epilepsy (QOLCE) questionnaire score (+1.0, $p < 0.001$), which was driven by changes in attention, behaviour, social interaction, other cognitive, stigma, physical restrictions and social activity domains. It should be noted that patients in the Krueger 2013 study had their current stable dose of AEDs throughout the study.

In the 48 month follow up study (Krueger, 2016), quality of life measured by the QOLCE composite score improved an average of 14% (43.7 ± 13.4 at baseline compared to 52.0 ± 17.8 after 48 months). There were positive changes in stigma, self-rated quality of life, attention/concentration, anxiety, language, and general health but the results did not reach statistical significance due to individual variation and cohort size. Trends in behaviour improvement in both positive and negative domains were also observed after 48 months of treatment, but similarly did not reach statistical significance. Patients in the Krueger 2016 extension study were allowed changes to their AED medication. For example, one patient stopped AED treatment during the extension phase of the Krueger study and maintained seizure control with everolimus alone. However, the overall number of AEDs used by patients during the 48 months remained unchanged (median 5.2, range 0–4).

Safety and tolerability

Evidence from the phase III extension study (Franz, in press) which studied 361 patients up to 2 years indicated 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. Grade 3 or 4 adverse events were reported in 145 patients (40.2%) and most frequent ($\geq 2.5\%$) were pneumonia (6.9%), status epilepticus (3.3%), seizures (2.8%), and stomatitis (2.5%). 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 (one due to pneumonia and one due to septic shock; both in children).

There is limited long term evidence (2 years or more) for everolimus use in people with TSC related refractory focal onset seizures. Therefore, consideration should be given to regular monitoring of patients receiving everolimus beyond 2 years for TSC-related refractory focal onset seizures in order to promptly identify any adverse effects of treatment with everolimus.

As everolimus was evaluated as an add-on to current treatment, it is not intended to replace current therapies. Therefore comparative evidence does not exist.

6 Documents which have informed this Policy

The documents that have informed this policy include a review of the clinical evidence available for everolimus. Additional evidence sources are listed in the reference section below.

7 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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