Clinical Commissioning Policy Proposition:

Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 and above)

Reference: NHS England 1700

Prepared by the National Institute for Health and Care Excellence (NICE) Commissioning Support Programme

Published by NHS England, in electronic format only.

Contents

1 Executive Summary

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 8.8 to 10 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 (individually or in combination), 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]).

About the new treatment

Everolimus is a drug that targets a pathway that regulates cell growth and multiplication. In patients with TSC, 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. It has 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 (individually or in combination).

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 (individually or in combination), 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. We have concluded that there is enough evidence to consider making the treatment available.

Everolimus may be given to 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 in addition to their current treatments and where surgical resection has already been considered.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission everolimus as an add-on treatment for people aged 2 years and older with refractory focal onset seizures associated with tuberous sclerosis complex (TSC).

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether everolimus will be routinely commissioned for this indication will made by NHS England following a recommendation from the Clinical

Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

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 between 1,471 and 2,925 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 (Votubia) is a disease modifying drug in TSC that targets the mammalian target of rapamycin (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. It is 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' (EMEA/H/C/002311 -II/0044 2017). It is administered orally. Dosage depends on body surface area and age.

Everolimus is also licensed by the European Medicines Agency:

- 'for the treatment of adult patients with renal angiomyolipomas (kidney tumours) associated with TSC' and has been shown to stop kidney tumours from growing and causing complications; and
- 'for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with TSC who require therapeutic intervention but are not amenable to surgery'.

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

4 Definitions

- Adjunctive – 'add on'
- Everolimus (Votubia) – 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.
- mTOR (mammalian target of rapamycin) – 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. It enables to determine 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.

5 Aims and Objectives

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

The objectives were to:

- ensure evidence based commissioning with the aim of improving outcomes for patients with refractory focal onset seizures associated with TSC in people aged 2 years and older; and
- identify clinical criteria for treating patients with refractory focal onset seizures associated with TSC in people aged 2 years and older.

6 Epidemiology and Needs Assessment

The estimated prevalence of the condition in the UK ranges between 8.8 per 100,000 (O'Callaghan et al., 1998) up to 10 in 100,000 (Committee for Medicinal Products for Human Use, European Medicines Agency, 2011).

Based on this, it is estimated there are between 4,900 and 5,500 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 between 4,100 and 4,600 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 between 1,500 and 3,000 people. See table below.

Estimates	Data source	Number of people
Population in England in mid-2016	Office for National Statistics	55,268,100
8.8 to 10 in 100,000 with TSC	Previous NHS England clinical policies on SEGA and AML, and company submission	4,864 – 5,527
Epilepsy is in 84% of TSC patients	(Kingswood et al, TOSCA data, 2017) – from company submission	4,086 – 4,643
Refractory to treatment - 36% to 63%	(Kingswood et al, TOSCA data, 2017) – from company submission (Chu-Shore et al. 2010)	1,471 – 2,925

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). Generalized 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).

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of everolimus for the treatment of people aged 2 years and older with refractory focal onset seizures associated with TSC, 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.

Seven studies were included in the clinical evidence review. Of those, 2 studies formed the main evidence for this policy: 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 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 (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.

Behaviour and quality of life

The French study investigators had intended to report the effect of everolimus on patient behaviour using the Vineland Adaptive Behavior 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 Behavior 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 to 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 what the most frequent treatment-related adverse effects were. As stated above, the safety and tolerability from the Franz et al. study (in press) has 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.

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.

8 Proposed Criteria for Commissioning

NHS England has concluded that there is sufficient clinical evidence to support a proposal for the routine commissioning of everolimus as add-on treatment of refractory focal onset seizures with or without secondary generalisation associated with TSC in people aged 2 years and older, 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.

Criteria for starting treatment:

- Patients aged 2 years and older: with a confirmed diagnosis of TSC related seizures whose refractory partial-onset seizures (focal onset seizures), with or without secondary generalisation (focal to bilateral tonic clonic seizures), are associated with TSC; AND
- whose TSC-related seizures have not adequately responded (meaning 2 or more partial onset seizures per month OR recurrent status epilepticus to treatment with at least 2 different AEDs titrated to a therapeutic dose (individually or in combination); AND
- who have previously been considered for surgical resection as assessed by a designated Children's Epilepsy Surgery Service (CESS). Specifically, the CESS will have previously decided that:

    - there is no brain abnormality which can be identified as causing seizures that can be removed surgically without unacceptable risks; OR
    - there are multiple or infiltrative brain abnormalities which may be causing seizures which cannot be removed surgically; OR
    - surgery has been performed and the seizures have not adequately reduced in frequency or severity;
- AND who have been considered for VNS and:
    - VNS was not considered appropriate as the next treatment option by the patient, or their carer in discussion with the treating clinician; OR
    - VNS has been performed and seizures have not adequately reduced in frequency or severity
- AND for whom, in the opinion of a properly constituted multi-disciplinary team (MDT) (as defined in the governance arrangements), everolimus is considered more appropriate than a trial of an alternative AED (in line with NICE CG137 which states that treatment strategies should be individualised).

Refractory means seizures that occur in spite of therapeutic levels of anti-epileptic drugs or seizures that cannot be treated with therapeutic levels of anti-epileptic drugs because of intolerable adverse side effects.

Everolimus will not be routinely commissioned as a first-line treatment.

Stopping Criteria:

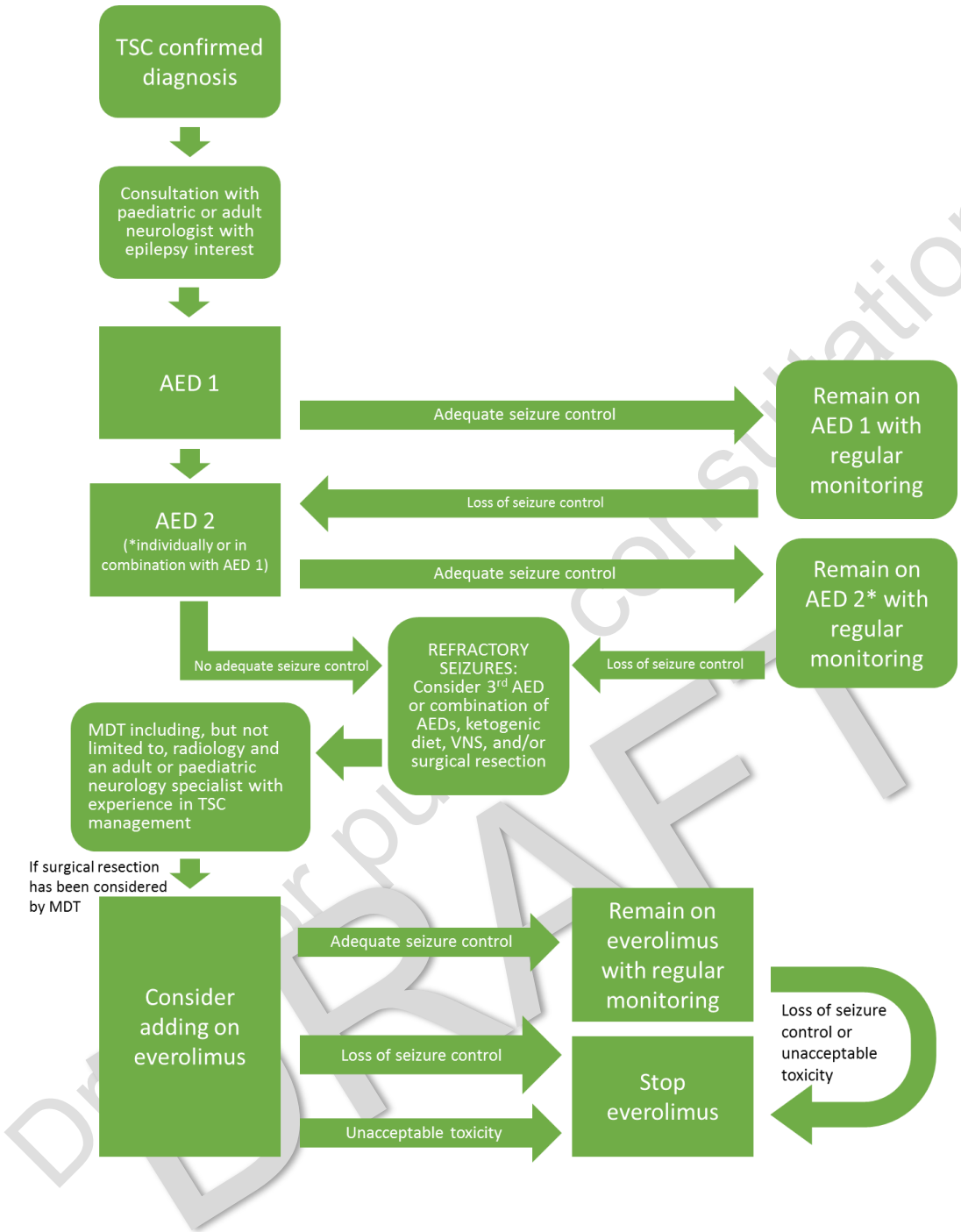
Everolimus treatment should be discontinued:

i. if the frequency or severity of seizures has not been reduced by at least 50% at 28 weeks based on seizure diaries collected by the patient (or parent/carer) or assessment by a neurologist with a specialty interest in epilepsy which takes account of the patient's full medical history; OR

ii. if unacceptable toxicity with everolimus has been experienced.

9 Proposed Patient Pathway

Figure 1 Treatment pathway for refractory TSC related seizures



Once it is confirmed that a patient has a definite diagnosis of TSC, if the person has TSC-related seizures, the patient will then be prescribed an anti-epileptic drug (AED) by a paediatric or adult neurologist, depending on the age of the patient. The AED is slowly increased to a therapeutic dose over several weeks. If noticeable seizures do not reduce to an acceptable level, the patient will be prescribed a

different or additional AED also increased to a therapeutic dose (see figure 1).

Treatment of refractory seizures

If a patient's seizures do not reduce in severity and frequency after having received 2 different and appropriate AEDs at therapeutic doses (individually or in combination) the seizures would then be considered refractory (in other words, not responding to AED treatment). Patients with refractory seizures related to TSC should be referred to an adult or paediatric neurologist specialising in epilepsy (if they have not yet been referred to one) and must be considered for the following treatments before everolimus is considered including:

- a different AED or a combination of AEDs
- a ketogenic diet
- Vagal Nerve Stimulation (see NHS England's clinical commissioning policy: Vagal Nerve Stimulation for Epilepsy, April 2013 [Ref: NHSCB/D04P/d]) or
- surgical resection (see NHS England's Children's Epilepsy Surgery Service Specification, November 2016 [Ref: E09/S/e]).

This clinical policy should be read in conjunction with NHS England's Children's Epilepsy Surgery, Paediatric Neurosurgery and Paediatric Neurology service specifications and NICE clinical guideline on epilepsies: diagnosis and management (CG137).

Prescription and monitoring of everolimus is determined by an adult or paediatric neurologist specialising in epilepsy within a properly constituted MDT (as defined in the Governance Arrangements). A care plan must be agreed with anticipated targets of improvement, specifically including seizure diaries collected by the patient (or parent/carer) or assessment by a neurologist with specialist interest in epilepsy which takes account of the patient's full medical history. The MDT may specify additional outcome criteria on a per-patient basis where felt appropriate such as reduction in hospital admission frequency, use of rescue medications, or reduction in the number of falls. Everolimus will not be prescribed as a first treatment for TSC-related refractory seizures.

10 Proposed Governance Arrangements

Everolimus will be available following discussion and agreement by a properly constituted MDT including, but not limited to, a radiologist, and a neurology specialist with experience in TSC management (paediatric or adult, as appropriate) and therapeutic drug monitoring.

Any provider organisation treating patients with this intervention will be required to assure that the internal governance arrangements have been completed before the medicine is prescribed. This should include detailing the process for MDT discussion, for which logistical details may differ between sites. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using software such as an electronic prior approval system and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined. For patients who have not been treated using VNS prior to everolimus treatment, a record that documents that VNS has been considered, discussed and the reasons for not proceeding with VNS should be included on the system.

11 Proposed Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

12 Proposed Audit Requirements

Specialised centres will be required to ensure that processes are in place to track decision to treat and evidence of effectiveness, e.g. trough level monitoring, seizure reduction or other clinical benefit. Centres may use software systems to track and audit use of everolimus, in order to ensure it is administered according to the Criteria for Commissioning.

13 Documents That Have Informed This Policy Proposition

The documents that have informed this policy proposition include a review of the clinical evidence available for everolimus and a submission from Novartis. Additional evidence sources are listed in the table of references below.

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

15 References

Amin, S., Lux, A., Calder, N., Laugharne, M., Osborne, J. and O'Callaghan, F. (2016) Causes of mortality in individuals with tuberous sclerosis complex. *Developmental Medicine & Child Neurology*, 59(6) pp. 612-617.

Bombardieri, R., Pinci, M., Moavero, R., Cerminara, C. and Curatolo, P. (2010). Early control of seizures improves long-term outcome in children with tuberous sclerosis complex. *European Journal of Paediatric Neurology*, 14(2): pp146–149.

Chu-Shore, C.J. Major, P., Camposano, S., Muzykewicz, D. and Thiele, E.A., (2010). The natural history of epilepsy in tuberous sclerosis complex. *Epilepsia*, 51(7) pp 1236-1241.

ClinicalTrials.gov [Internet] Bethesda (MD): National Library of Medicine (US) 2017 August 24. Identifier NCT01713946. Novartis: A Placebo-controlled Study of Efficacy & Safety of 2 Trough-ranges of Everolimus as Adjunctive Therapy in Patients With Tuberous Sclerosis Complex (TSC) & Refractory Partial-onset Seizures (EXIST-3). Available from https://clinicaltrials.gov/ct2/show/NCT01713946

Crall, C., Valle, M., Kapur, K., Dies K.A., Liang, M.G., Sahin, M. and Huang, J.T. (2016) Effect of Angiofibromas on Quality of Life and Access to Care in Tuberous Sclerosis Patients and Their Caregivers. *Pediatric Dermatology*, 33(5), pp 518-525.

European Medicines Agency (2017) EMA/ H/C/002311-II/0044 Votubia: EPAR – Product Information: Annex I Summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002311/WC500112238.pdf, October 2017.

Fisher, R.S. Cross, J.H., D'Souza, C., French, J., Haut, S.R., Higurashi, N., Hirsch, E., Jansen, F.E., Lagae, L., Moshe, S.L. Peltola, J., Roulet Perez, E., Scheffer, I.E., Schulze-Bonhage, A., Somerville, E., Sperling, M., Yacubian, E.M. and Zuberi, S.M. (2017) Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*, 58(4), pp 531-542.

Franz, D.N., Belousova, E., Sparagana, S., Martina Bebin, E., Frost, M.D., Kupermen, R., Witt, O., Kohrman, M.H., Flamini, J.R., Wu, J.Y., Curatolo, P. de Vries, P.J., Berkowitz, N., Niolat, J., and Jóźwiak, S. (2016) Long-Term Use of Everolimus in Patients with Tuberous Sclerosis Complex: Final Results from the EXIST-1 Study. *PLoS ONE* 11(6) https://doi.org/10.1371/journal.pone.0158476, October 2017.

French, J., Lawson, J., Yapici, Z., Ikeda, H., Polster, T., Nabbout, R., Curatolo, P., de Vries, P., Dlugos, D., Berkowitz, N., Voi, M., Peyrard, S., Pelov, D. and Franz, D. (2016). Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *The Lancet*, 388(10056), pp 2153-2163.

French, J. and Staley, B.A. (2012) AED Treatment Through Different Ages: As Our Brains Change, Should Our Drug Choices Also? *Epilepsy Currents*, 12 (Suppl. 3; pp 22-27.

Hesdorffer, D.C., Tomson, T., Benn, E., Sander, J.W., Nilsson, L., Langan, Y., Walczak, T.S., Beghi, E., Brodie, M.J. and Hauser, A. (2011) Combined analysis of risk factors for SUDEP. *Epilepsia*; 52(6) pp 1150-9.

Krueger, D.A., Wilfong, A.A., Holland-Bouley, K., Anderson, A.E., Agricola, K., Tudor, C., Mays, M., Lopez, C.M., Kim, M-O., and Franz, D.N. (2013) Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. *Annals of neurology* 74, 679-87.

Krueger, D.A., Wilfong, A.A, Mays. M., Talley, C.M., Agricola, K., Tudor, C., Capal, J., Holland-Bouley. K., and Franz, D.N. (2016) Long-term treatment of epilepsy with everolimus in tuberous sclerosis. *Neurology* 87, 2408-2415.

Lamberts, R.J., Thijs, R.D., Laffan, A., Langan, Y. and Sander, J.W. (2012) Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia*, 53(2): pp 253-7.

Muzykewicz, D.A., Newberry, P., Danforth. N., Halpern, E.F. and Thiele, E.A. (2007) Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis complex. *Epilepsy & Behavior*, 11(4), pp 506-513.

National Institute for Health and Care Excellence. (2016). Epilepsies: diagnosis and management. NICE guideline (CG137) United Kingdom.

Northrup, H. and Krueger, D.A. (2013) Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatric Neurology*, 49: pp 243-254.

O'Callaghan, F.J.K., Shiell, A.W., Osborne, J.P. and Martyn, C.N. (2008). Prevalence of tuberous sclerosis estimated by capture-recapture analysis. *The Lancet,* 351: p1490.

Ryvlin, P., Nashef, L., Lhatoo, S.D., Bateman, L.M., Bird, J., Bleasel, A., Boon, P., Crespel, A., Dworetzky, B.A., Høgenhaven, H., Lerche, H., Maillard, L., Malter, M.P., Marchal, C., Murthy, J.M., Nitsche, M., Pataraia, E., Rabben, T., Rheims, S., Sadzot, B., Schulze-Bonhage, A., Seyal, M., So, E.L., Spitz, M., Szucs, A., Tan, M., Tao, J.X., and Tomson, T. (2013). Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurology*, 12(10), pp 966-77.

Thompson, P.J. and Duncan, J.S. (2005). Cognitive Decline in Severe Intractable Epilepsy. *Epilepsia,* 46(11), pp1780–1787.
Wang, S and Fallah, A. (2014). Optimal management of seizures associated with tuberous sclerosis complex: current and emerging options. *Neuropsychiatric Disease and Treatment,* 10: pp2021–2030.

END