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

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

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Contents

Policy Statement

NHS England will commission everolimus as an add on treatment of people aged 2 and above who have tuberous sclerosis related seizures in accordance with the criteria outlined in this document.

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.

This policy document outlines the arrangements for funding of this treatment for the population in England.

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, mammalial 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 vagus nerve stimulation (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 make 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.

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 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, 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' (EMEA/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 converts 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 (VNS) - 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 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.

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

Estimated uptake Adults 10% Children 75%	Scottish Medicines Consortium: everolimus 2mg, 3mg and 5mg dispersible tablets (Votubia®) SMC No 1331/18: 4 May 2018	100 237

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 measured 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

NHS England has concluded that there is sufficient evidence to support 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, two 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.

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 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 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, 103 (28.5%) had less than 2 years of follow-up at study cut-off and 40% were exposed to everolimus for more than two 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. Whilst this study shown sustained reduction in seizures the data should be interpreted with caution and take into account the patient withdrawals, the lack of a control arm and the lack of assessments related to change in AEDs usage.

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 includes 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) 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 (≥2.5%) were pneumonia (6.9%), status epilepticus (3.3%), seizures (2.8%), and stomatitis (2.5%). Pneumonia is a major cause of morbidity and mortality in children younger than five whilst renal disease and SUDEP are considered significant causes of morality in TSC. 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.

With each additional AED in polytherapy and higher drug load there is a significant decrease in performance of executive functions as well as significant adverse effects on cognition. 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 Criteria for Commissioning

NHS England has concluded that there is sufficient clinical evidence to support the routine commissioning of everolimus dispersible tablets 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; AND
- who have previously been considered for surgical resection as assessed by a designated Children's Epilepsy Surgery Service (CESS) or adult specialised epilepsy surgery service. Specifically, the CESS / specialised adult service 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.

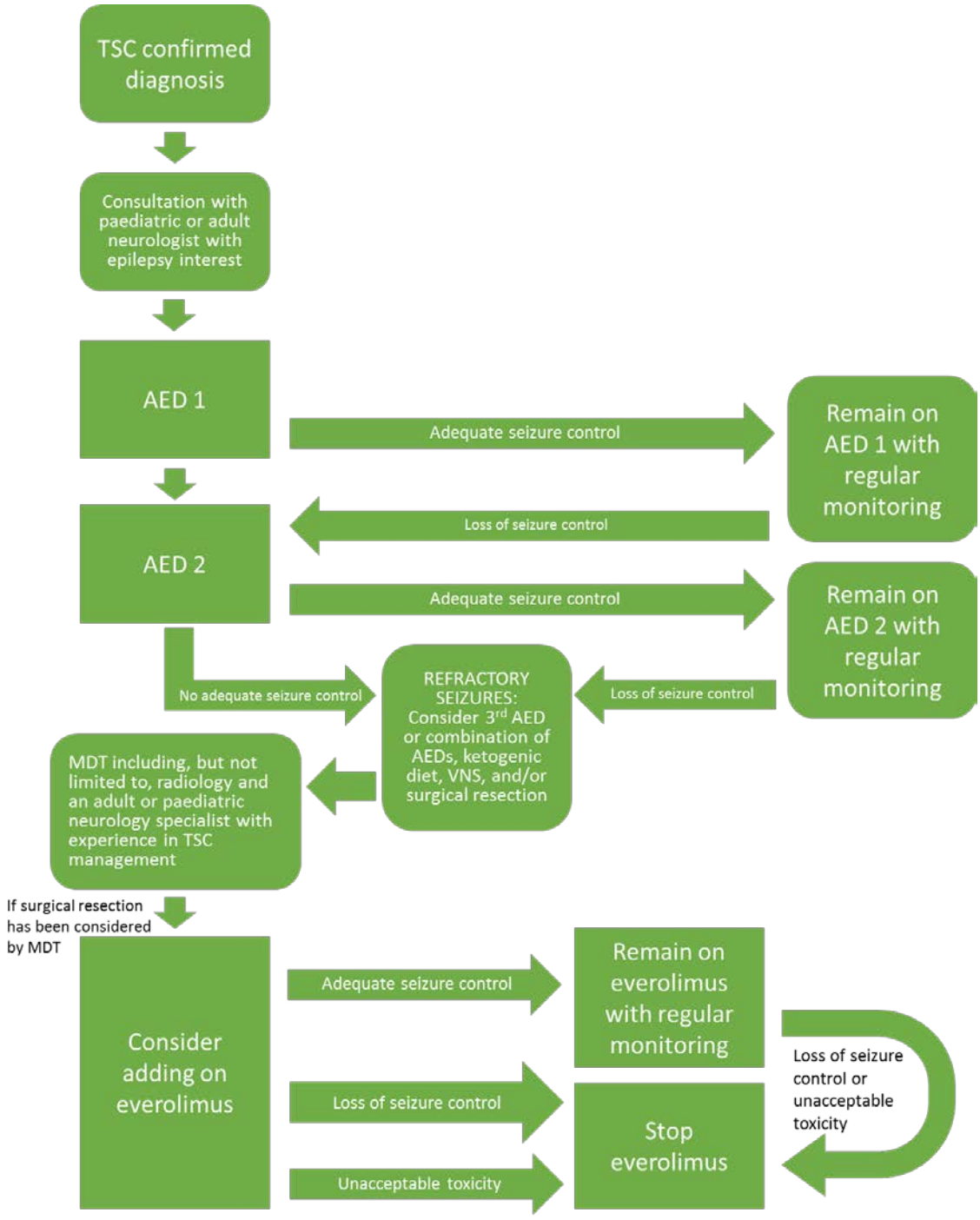
Stopping Criteria:

Everolimus treatment should be discontinued:

- 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
- if unacceptable toxicity with everolimus has been experienced.

7 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 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). Consideration should be given to the local availability of services to undertake blood tests to support monitoring arrangements and reduce the number of additional appointments at the specialised centre that patients are required to attend. Local reporting arrangements need to be in place to ensure that results can be sent to the specialised centre for review in time for the patient's next outpatient appointment with the specialised team. 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 it is 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 line treatment for TSC-related refractory seizures.

8 Governance Arrangements

Everolimus dispersible tablets 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.

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.

9 Mechanism for Funding

Everolimus is no longer listed on the NHS Payment Scheme Annex A (high-cost drugs), so use of this drug is in-tariff.

10 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. through trust 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.

11 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 table of references below.

12 Date of Review

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

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