NHS England

Clinical Commissioning Policy: Everolimus for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex

Reference: NHS England: 16066/P

NHS England INFORMATION READER BOX		
Directorate		
Medical Nursing Finance	Operations and Information Trans. & Corp. Ops.	**Specialised Commissioning** Commissioning Strategy

Publications Gateway Reference:	**05527s**
Document Purpose	Policy
Document Name	[illegible] associated with tuberous sclerosis complex
Author	Specialised Commissioning Team
Publication Date	12 December 2016
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	Routinely Commissioned - NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	N/A
Superseded Docs (if applicable)	N/A
Action Required	N/A
Timing / Deadlines (if applicable)	**N/A**
Contact Details for further information	england.specialisedcommissioning@nhs.net

Document Status

This is a controlled document. Whilst this document may be printed, the electronic version posted on the intranet is the controlled copy. Any printed copies of this document are not controlled. As a controlled document, this document should not be saved onto local or network drives but should always be accessed from the intranet.

Clinical Commissioning Policy: Everolimus for ependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex

First published: November 2016

Prepared by NHS England Specialised Services Clinical Reference Group for Paediatric neurosciences

Published by NHS England, in electronic format only.

Contents

1 Introduction 7
2 Definitions 8
3 Aims and Objectives 8
4 Epidemiology and Needs Assessment 9
5 Evidence Base 10
6 Documents which have informed this Policy 12
7 Date of Review 15
References 16

Policy Statement

NHS England will routinely commission the use of everolimus for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex 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.

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 tuberous sclerosis complex and SEGAs

Tuberous sclerosis complex (TSC) is a genetic condition, present from birth. It can lead to non-cancerous growths developing in a number of different organs of the body. The organs most commonly affected are:

- brain
- eyes
- heart
- kidney
- skin

- lungs.

It is estimated that around 1 in every 6,000 babies are born with the condition. However, in many cases the diagnosis cannot be made until later in life when symptoms become more apparent. Usually this is in childhood.

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. In many cases, and with the appropriate medical care, people with TSC can expect to live healthy lives with a normal life expectancy.

Subependymal giant cell astrocytomas (SEGAs) are a type of non-cancerous growth in the brain that can be caused by TSC.

About the current treatment

Surgery is the standard treatment for SEGAs. However, they are often found deep in the brain and this can mean that they can be difficult or impossible to remove. Surgery may lead to complications. It is also possible that surgery fails to remove all of the growth.

About the new treatment

For patients with TSC who develop SEGAs that cannot be removed by surgery, they can be given a medicine to reduce the size of the SEGA, such as everolimus. Everolimus works by reducing the size and slows the growth of the SEGA.

What we decided

NHS England has carefully reviewed the evidence to treat patients with TSC who develop SEGAs that cannot be removed by surgery with everolimus. We have concluded that there is enough evidence to consider making the treatment available.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission everolimus for the specific group of patients with SEGAs which are not amenable to surgery.

Tuberous sclerosis complex (TSC) is a genetic disease characterised by the formation of multiple benign tumours (hamartomas) throughout the body. The clinical signs and symptoms of the disease are caused by the hamartomas. There are several major clinical problems that occur in patients with the disease including epilepsy, learning difficulties, psychopathology, renal angiomyolipomas with associated bleeding and subependymal giant cell astrocytomas (SEGAs).

SEGAs are benign, slow-growing brain tumours. They can be solitary or multiple and usually form within the ventricles near the foramen of Monro, an opening deep in the brain that drains cerebrospinal fluid. They are usually asymptomatic until they grow large enough to block circulation of the cerebrospinal fluid (CSF), leading to hydrocephalus (a build-up of fluid on the brain). Common symptoms of SEGAs include headaches, nausea, vomiting, seizures, behavioural changes, and visual problems.

Surgery is the standard treatment for SEGAs; however, due to their deep location they can be difficult or impossible to resect, leading to complications or incomplete clearance. The risk of mortality or permanent serious post-operative complications increases in parallel to the difficulty of the surgery.

Everolimus, a rapamycin analogue, is a disease modifying drug in TSC. It reduces tumour volume with respect to SEGAs and reports benefits on the distressing facial rash (facial angiofibromatosis). It acts by inhibiting mTOR (a major cell growth and proliferation controller), which is over-activated in individuals with TSC. It is licensed by the European Medicines Agency to treat SEGAs in adults and children whose brain tumour cannot be surgically removed (EMA/682567/2015). Dosage depends on body surface and age; a starting dose of 7mg/m^2 is recommended for ages 1 to less

than 3 and 4.5mg/m² for ages 3+ (as per manufacturer's guidelines). Treatment may last for many years, since everolimus is not curative.

2 Definitions

Tuberous sclerosis complex (TSC) is a genetic disorder which is characterised by the development of multiple benign tumours (hamartomas), mainly in the brain, kidney, liver, skin, heart and lung.

Subependymal giant cell astrocytomas (SEGAs) are benign, slow-growing brain tumours that are almost exclusively associated with TSC and develop in 5-20% of TSC patients usually during childhood and adolescence.

Rapamycin is a drug characterised primarily by its ability to suppress the immune system.

mTOR (mammalian target of rapamycin) is a molecule that regulates cell growth proliferation.

Everolimus (Votubia) is an analogue of rapamycin. It acts by inhibiting mTOR, which is overactivated in individuals with TSC.

3 Aims and Objectives

This policy proposition aims to define NHS England's commissioning position on everolimus as part of the treatment pathway for patients with SEGAs associated with TSC that are not amenable to surgery.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for patients with SEGAs associated with TSC that are not amenable to surgery.

4 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.

Based on this, there could be up to 5,425 patients in England with TSC. However, this is likely to be an underestimation of the true prevalence, because diagnosis depends on clinical features that are variable and prevalence is increasing with better identification of less severe cases.

Of those that have TSC, between 5% and 20% are estimated to develop SEGAs (including both symptomatic and asymptomatic). Based on this, the number of people with SEGAs due to TSC in England is estimated at between 271 and 1,085.

Of those who have SEGAs, an estimated 50% may not be amenable to surgery (evidence from clinical practice) – these patients may be eligible for everolimus. Table 1 sets out the epidemiological modelling, in accordance with the commissioning criteria and clinical judgment.

The majority of SEGA cases are in patients aged 20 years or younger, although patients may present as late as 40 (evidence from clinical practice).

Table 1

Cohort	Criteria	Patients
a) Total population with TSC	1 case TSC per 10,000 population (All ages) (EMA, 2011)	5452
b) Proportion with SEGA	5% to 20% of TSC patients develop SEGAs	271 – 1085
c) Potential eligibility for treatment everolimus	Those with SEGAs not amenable to surgery – 50% of cohort b (based upon clinical judgement)	136 – 542
d) Clinically likely to commence treatment per-year	7% of patients (5% who are symptomatic + likely increase based on clinical judgement)	10 – 38
e) Continuing with treatment post year 1	6.5% stop treatment due to side-effects, adverse reactions or developing resistance to the drug (Franz et al, 2014)	9 – 36

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the specific group of patients for which there is no other curative treatment. The evidence shows that everolimus reduces the size of SEGAs.

EXIST-1(Franz D et al 2013), a relevant randomised controlled trial, assessed the effectiveness of everolimus in patients with SEGA associated with TSC. The trial was well conducted with 117 patients, although some power was lost as patients were randomised in a 2:1 ratio to everolimus versus placebo, presumably to encourage patients to enter the trial. To be included, patients had to have evidence of worsening SEGA, but be unlikely to require surgery with no critical hydrocephalus. The median age of participants was 9.5 years and they were followed-up for a minimum of 6 months (median=9.7 months). The primary outcome was the proportion of patients

with SEGA response, which was defined as a reduction in the total volume of all target SEGA of 50% or more relative to baseline, in the absence of worsening of non-target SEGA, new lesions of 1cm or greater in diameter, and new or worsening hydrocephalus. Everolimus was found to be effective with 35% of patients (n=27/78) achieving SEGA response compared to none in the placebo arm (n=0/39) and no cases of progression compared to 15% of patients (n=6/39) in the placebo arm. In addition to its effect on SEGA, everolimus produced significant reductions in skin lesions and kidney tumours. Adverse events were common and although mostly not serious, they caused half of all everolimus patients to temporarily halt treatment or reduce their dose. The most common adverse events were mouth ulceration and stomatitis, both of which were experience by around a third of all everolimus patients. In an open-label extension period of this trial (Franz D et al, 2016), all patients were given everolimus and followed up over 4 years. The effectiveness of everolimus in sustaining tumour volume reduction was maintained. The findings of the trial appear generalisable to a UK population.

While it is apparent from EXIST-1 and it's open-label extension that everolimus is effective at shrinking and stabilising SEGAs and this effect seems to be maintained in the medium term over 4 years with reasonable tolerability, it is difficult to currently assess its long term clinical and cost-effectiveness. EXIST-1 only offers randomised evidence for a median follow-up of 10 months as 6 months after the last patient was enrolled all patients in the placebo arm were crossed-over to everolimus – the open-label extension phase. Without a longer-term randomised comparison it is impossible to assess clinical effectiveness, for example how many untreated patients would have had no complications from SEGA or would have eventually been cured by surgery without complications. Questions remain about whether treatment with everolimus needs to be life-long, whether tumours will ultimately progress on treatment, and finally the long-term side effects. No reliable data on quality life were found and in the absence of reliable data on long-term clinical outcomes, cost-effectiveness cannot be established.

1 Is Everolimus clinically effective in reduction in SEGA tumour volumes and improvement of quality of life in patients with the Tuberous Sclerosis complex compared with no intervention or with other standardised treatments?

There is robust evidence from one well-conducted, moderately sized RCT to show that everolimus is effective at reducing SEGA tumours in the short-term compared to no treatment. The trial found that 35% of patients (n=27/78) in the everolimus arm achieved a reduction in the total volume of SEGA by 50% or more compared with 0% of patients (n=0/39) in the placebo arm (difference = 35% (95% CI = 15 to 52%, p<0.0001)). Changes in tumour volumes were not reported so the absolute changes in tumour size are not known. Patients were followed up for a median of ten months and then all placebo patients were crossed-over to everolimus in the open-label extension phase over four years. The effect of everolimus on quality of life is not known. No trials were found comparing everolimus to other mTOR inhibitors or surgery.

2 Is Everolimus cost effective in patients suffering from SEGA associated with TSC?

No studies were found assessing the cost-effectiveness of everolimus in patients with SEGA associated with TSC. In the absence of data on clinical effectiveness it is impossible to establish cost-effectiveness.

6 Criteria for commissioning

Inclusion criteria:

Patient presents with SEGA lesion(s) and has at least one lesion of baseline longest diameter 1cm as assessed by multiphase MRI and is considered not amenable to surgery as assessed by a properly constituted MDT (as defined in the Governance Arrangements). Specifically, MDT decides that:

(a) the SEGA is too difficult to remove surgically; OR
(b) SEGA needs reduction in size prior to surgery; OR
(c) SEGA lesion(s) are multiple or infiltrative; OR
(d) surgery has been performed and there is residual SEGA (i.e. it was not possible to completely excise) that needs treating.

AND

The patient presents with:

(i) significant growth in target SEGA lesion(s) (as decided by properly constituted MDT since patients' last annual MRI); OR

(ii) unequivocal worsening of non-target lesions of SEGA; OR

(iii) the appearance of new lesion(s) of baseline longest diameter 1cm; OR

(iv) symptoms of new or worsening hydrocephalus (but where urgent surgery is not required); OR

(v) patient presents for the first time with lesion(s) of baseline longest diameter 1cm (accounting for patients not cared for in a surveillance programme); OR

(vi) partially excised SEGA lesion(s) known to be growing before surgery.

Exclusion criteria:

Any patient presenting with raised intracranial pressure (a surgical solution would be necessary as it would not be possible to wait for mTOR inhibition to take effect).

Stopping criteria:

(i) Evidence of continued growth in volume of the target SEGA lesion (any, assessed by bi-annual MRI); OR

(ii) Evidence of appearance of one or more new SEGA lesions with a minimum longest diameter of 1cm; OR

(ii) Serious adverse effects; OR(iv) Acute worsening of hydrocephalus necessitating a surgical solution; OR

(v) Non-compliance indicated by blood levels despite reasonable efforts to educate patients/parents and/or secure regular drug administration.

7 Patient Pathway

Tuberous sclerosis is primarily diagnosed amongst children and young adults (<20), although patients may present as late as 40. Patients with TSC are monitored with annual multiphase MRI scans. If a SEGA lesion is detected, a multi-disciplinary team

(as defined in the Governance Arrangements) determines whether to continue to monitor the lesion through regular scans or perform surgery to remove the lesion.

Any patient presenting with raised intracranial pressure will need a surgical solution (either removal of SEGA or shunt insertion) as it would not be possible to wait for mTOR inhibition to take effect.

If the patient is not amenable to surgery (as defined in the Criteria for Commissioning), the MDT can prescribe everolimus. Everolimus will not be used first-line in patients who have acute symptoms.

Treatment is prescribed with an initial dose (a starting dose of 7mg/m² body surface area is recommended for ages 1 to less than 3 and 4.5 mg/m² for ages 3+) and titrated. Trough levels of everolimus should be monitored by the prescribing consultant after initiation of treatment, following dose changes, addition of concomitant medications or change in liver function. Primary care services may need to be involved in performing some routine blood tests (e.g. liver function tests) and treating any minor adverse events (such as mouth ulcers and stomatitis).

Everolimus is not curative and patients are likely to remain on the drug for many years.

8 Governance Arrangements

All cases must be discussed by a MDT consisting of oncology, radiology, neurosurgery and neurology (paediatric or adult, as appropriate). Preferably, a specialist in TSC would also be involved.

9 Mechanism for Funding

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

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. trough level monitoring). 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

European Medicines Agency, Everolimus (Votubia) license, EMA/682567/2015

12 Date of Review

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

References

O'Callaghan, FJK, Shiell, AW, Osborne, JP and Martyn, CN. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. Lancet May 1998; 351: p1490

Franz D, Belousova E, Sparagana S, Bebin E, Frost M, Kuperman R et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. The Lancet. 2013;381(9861):125-132

Franz et al, Long-term use of Everolimus in patients with Tuberous Sclerosis Complex: Final Results from the Exist – 1 Study PLoS ONE 11(6):e0158476 June 28, 2016