NHS England

Clinical Commissioning Policy Proposition:

Everolimus for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex

Reference: NHS England E09X04/01

DRAFT FOR PUBLIC CONSULTATION

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Plain Language Summary

The policy proposition aims to confirm NHS England's commissioning approach to everolimus for patients with tuberous sclerosis complex who develop subependymal giant cell astrocytomas that cannot be removed by surgery.

Tuberous sclerosis complex (TSC) is a genetic condition, present from birth, which can lead to non-cancerous growths developing in a number of different organs of the body. The organs most commonly affected are the brain, eyes, heart, kidney, skin and 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 relatively mildly affected and may not even know they have TSC, while others are much more significantly 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. Usually, SEGAs are removed by surgery, but sometimes they are too large or the surgery is not fully successful. In these cases, patients can be given a drug to reduce the size of the SEGA, such as everolimus. Everolimus works by inhibiting mTOR, a molecule which controls cell growth. In patients with TSC, mTOR is over-activated.

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of everolimus for patients with TSC who develop SEGAs that cannot be removed by surgery.

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.

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

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 patients with SEGAs associated with TSC that are not amenable to surgery is planned to be made by NHS England by June 2016, following a recommendation from the Clinical Priorities Advisory Group.

2. Proposed Intervention and Clinical Indication

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/m² is recommended for ages 1-to-≤3 and 4mg/m² for ages 3+ (as per manufacturer's guidelines). Treatment may last for many years, since everolimus is not curative.

3. 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.

4. Aim 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.

5. 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 1 in 10,000 (Committee for Medicinal Products for Human Use, European Medicines Agency, 2011).

Based on this, there could be up to 5425 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 1085.

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. (See next page)

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 (England, all ages)
a) Total population with TSC	1 case TSC per 10,000 population (All ages) (EMA, 2011)	5425
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 on 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	5% stop treatment due to side-effects, adverse reactions or developing resistance to the drug (Franz et al, 2014)	9 - 36
f) Current estimated activity (2014/15)	IFR applications in 2014/15, (number approved not known).	8

6. 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. Whilst the cohort of the RCT trial (EXIST-1) is not the same as the group of patients for which everolimus is proposed under this policy, the evidence does suggest that everolimus reduces the size of SEGAs.

We found one relevant RCT (EXIST-1), which assessed the effectiveness of everolimus in patients with SEGA associated with TSC. The trial was well conducted and of moderate size (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. The findings of the trial appear generalisable to a UK population.

While it is apparent from EXIST-1 that everolimus is effective at shrinking and stabilising SEGAs and this effect seems to be maintained over 3 years with reasonable tolerability, it is very difficult to truly assess its 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. 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. An ideal trial might randomise patients to everolimus or to a strategy of regular monitoring with surgery if indicated, and then follow these patients up for a long period time measuring clinical outcomes, such as hydrocephalus, seizures, cognition and quality of life. 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 so uncertainty remains around the long-term effectiveness of everolimus. The effect of everolimus on quality of life is not known as we only found one small case series measuring the outcome. 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.

7. Proposed 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 consituted MDT (as defined in section 9 - Proposed 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 consituted 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.

8. Proposed 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 Section 9 - Proposed 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 patient is not amenable to surgery (as defined in Section 7 - Proposed Criteria for Commissioning), 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-≤3 and 4mg/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.

9. Proposed 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.

10. Proposed Mechanism for Funding

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

11. 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. 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.

12. Documents That Have Informed This Policy Proposition

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

13. 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 (expected by June 2016).