Clinical Commissioning Policy Statement: Everolimus (Votubia®) for treatment of angiomyolipomas associated with tuberous sclerosis

NHS England Reference: [B14X09]

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Publications Gateway Reference:	**05222**
Document Purpose	Policy
Document Name	Clinical Commissioning Policy Statement: Everolimus (Votubia®) for treatment of angiomyolipomas associated with tuberous sclerosis
Author	Specialised Commissioning Team, NHS England
Publication Date	June 2016
Target Audience	
Additional Circulation List	
Description	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Superseded Docs (if applicable)	n/a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

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Contents

1 Plain Language Summary

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's 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, with some people being relatively mildly affected and may not even know they have TSC, while some are much more significantly affected. In many cases, and with the appropriate medical care, people with TSC can expect to live healthier lives with a normal life expectancy.

TSC growths have a different name depending on which organ they develop in. Angiomyolipoma (AML) growths are normally found in the kidney, but can also affect the liver. Though AML growths can be asymptomatic, they can also have life-threatening consequences due to their impact on kidney function and the risk of haemorrhage (Bissler 2012). AMLs are the leading cause of morbidity and mortality in adult TSC patients (Shepherd 1991, Dixon 2011).

Everolimus (Votubia®) is a licensed treatment for adults with TSC-associated AMLs. It is a relatively new type of drug called an mTOR inhibitor which has the potential to improve care because it can reverse the underlying abnormality in cells affected by the genetic mutation and has been shown to stop kidney tumours (AMLs) from growing and causing problems.

NHS England has reviewed the evidence and concluded that it is sufficient to enable everolimus (Votubia®) to be routinely commissioned and therefore available to children from three years of age and adults with TSC-associated AMLs, in accordance with the criteria outlined within this policy statement. Everolimus (Votubia®) is licensed to treat adults with TSC-associated AMLs, however the treatment is un-licensed for the paediatric age-range.

2 Background

Adults with TSC may have their care managed by a variety of different specialists (Neurologist, learning disability or general psychiatrist, chest physician, clinical geneticist, dermatologist, nephrologist or urologist) or their General Practitioner (GP). Where advice is needed about the management of renal disease, adult patients are referred onto a nephrologist or urologist. The care pathway for children with TSC usually involves regular follow-up by a general paediatrician or neuropaediatrician, who will monitor kidney health and refer them to a paediatric or adult nephrologist or urologist for advice on management of renal complications.

In English healthcare settings, the current commissioned first choice intervention for management of AMLs is percutaneous embolisation with surgical intervention second choice (Bissler 2004, Ewalt 2005). For AMLs presenting with acute haemorrhage, first-line therapy is embolisation followed by treatment with corticosteroids (Krueger 2013). The aim of embolisation is to reduce the risk of haemorrhage but it also causes tumours to diminish in size (Williams 2006). However there is a high recurrence rate and tumours continue to grow and bleed post embolisation (Bissler 2002).

The use of embolisation in this patient population was the subject of a retrospective study (Eijkemans et al, 2015). This study reviewed 351 adult patients treated consistently in a single centre over 16 years with pre-emptive embolisation. Ultimately this strategy failed to prevent renal failure and renal related deaths;

- 144/244 (59%) of patients with AMLs developed Chronic Kidney Disease (CKD) stage 3 or more;
- 57 (49%) of the 117 who had embolisation needed 2 or more embolisations,
- 14 (12%) of patients ended up in end stage renal failure; and
- 9 (8%) people passed away from renal related complications.

2.1 Proposed Intervention

Everolimus (Votubia®) was designated as an 'orphan medicine' by the European Medicines Agency in 2010 and is licensed for:

> "the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery" (European Medicines Agency 2010).

The use of everolimus (Votubia®) is not licensed in children for TSC-associated AMLs.

Additionally, mTOR inhibitors are recommended in the International Tuberous Sclerosis Committee Consensus Group 'Recommendations for the surveillance and management of tuberous sclerosis complex' for asymptomatic, growing AMLs measuring larger than 3cm in diameter (Krueger 2013). This is largely because patients almost always have multiple, bilateral AMLs (Sooriakumaran 2010) and use of an mTOR can minimise the deleterious effects on renal function.

2.2 Epidemiology and eligibility modelling

The prevalence of TSC in EU countries is estimated to be up to 1 in 10,000 head of population, a figure supported by the Committee for Medicinal Products for Human Use (European Medicines Agency 2011).

Based on data from the Office of National Statistics, the estimated UK population in 2013 is 63.5 million, of whom approximately 80% are aged 18 years or over. Thus, the number of TSC patients aged 18 years or older in the UK in 2013 is in the region of 5,000 (European Medicines Agency 2011, Office for National Statistics, 2015).

Because the prevalence of angiomyolipomas in TSC is 80% there could be over 5,000 TSC-angiomyolipoma patients in the UK, most with non-symptomatic tumours at any given time.

It is therefore expected that, in accordance with the commissioning criteria, the potential patient cohort in England requiring access to everolimus (Votubia®) will be in the region of 30 per year. Table 1 sets out the epidemiological modelling, in accordance with the commissioning criteria. It should be noted that annual numbers are based on the Clinical Expert Group assessment of the available epidemiology and known cohort eligible to current services. This approach has been taken to mitigate the lack of robust population based studies, and caveats in the literature including possible selection bias and other methodological differences.

Table 1: Epidemiological and eligibility modelling (all ages)

Cohort	Prevalence	Maximum Patient numbers (England)
a) Total population	1 case TSC per 10,000 population (All ages) (EMA, 2011)	5,525
b) Proportion accessing services	70% of TSC patients present with AML (Curatolo 2008)	3,868
c) Potential eligibility for treatment everolimus (Votubia®)	30%-40% multiple AMLs >30mm (Kingswood et al 2013)	1,160
d) Clinically likely eligibility to meet policy criteria	Pre-emptive treatment to prevent renal haemorrhage 9-22% (O'Callaghan 2004, Eiijkemans, 2015, Kingswood 2014)	348 – 850
e) Clinically likely to commence treatment per-year	Based on 16 year follow up of 'cohort d'	21 – 53
f) Clinically eligible per-year based on current services data	Clinically likely cohort estimated by clinical expert group meeting proposed criteria and accounting for discontinuation rate in section 3.1.	30

3 Commissioning Position

NHS England will commission everolimus (Votubia®) for treatment of TSC-associated AMLs in children (≥ 3years old) and adults, 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 statement outlines the arrangements for funding of this treatment for the population in England.

1. Angiomyolipomas (AMLs) which are 30 mm or greater and which demonstrate interval growth (Krueger 2013).

The contraindications for the use of everolimus (Votubia®) are:

1. Acute bleeding. This should be treated with embolisation first to gain haemostasis (Krueger 2013).
2. Females of childbearing potential must use a highly effective method of contraception while receiving everolimus, and for up to 8 weeks after ending treatment.
3. Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients.
4. Hepatic impairment in children.

All clinicians are advised to refer to the Summary of Product Characteristics for Votubia® for up to date information as to the caveats and precautions.

3.1 Dose

The recommended dose of everolimus (Votubia®) is 10mg once daily for adults. The dose should be adjusted in hepatic impairment and/or if the patient has an adverse reaction and/or there is a drug interaction (please refer to the Summary of Product Characteristics for recommended adjustments).

Everolimus (Votubia®) is unlicensed for the treatment of children with TSC-associated AMLs. The recommended dose to treat these cases is drawn from the treatment of SEGA, which is another condition associated with TSC. Dosing must be individualized and based on Body Surface Area using the Dubois formula. The recommended starting dose for children (≥ 3 years old) is 4.5mg/m^2 daily, careful titration is required to ensure optimal treatment.

Everolimus whole blood trough concentrations should be assessed at least 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 5-15 ng/ml. The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability.

3.2 Stopping criteria

Stabilisation and reduction in size of renal angiomyolipoma and the non-occurrence of renal bleeding; while preserving renal function are the main aims of treatment. This is monitored clinically and with MRI scan of the kidney. If the treatment with everolimus (Votubia®) fails to deliver these outcomes it should be stopped. Progression was defined within EXIST 2 as ≥ 25% increase from nadir in angiomyolipoma volume or ≥20% increase from nadir in the volume of either kidney with a value greater than baseline, appearance of new angiomyolipoma ≥ 1cm, or grade ≥ 2 angiomyolipoma-related bleeding).

If the renal angiomyolipoma(s) has not stabilised (i.e., ceased to grow) after 6 months of treatment with everolimus (Votubia®) at the maximum tolerated dose up to a maximum dose of 10mg daily, the treatment will be deemed to have failed and must be discontinued. A renal MRI scan should be performed in order to assess whether the renal angiomyolipoma has ceased to grow.

Bleeding and/or the need for embolisation or surgical intervention indicate that treatment has failed and therefore must be discontinued.

If a patient demonstrates a progressive fall in glomerular filtration rate (GFR) of below 30 mls/min, or a progressive increase in proteinuria of greater than 3g/L, despite dose adjustment, then treatment must be discontinued.

Intractable unacceptable side effects despite dose adjustment will be deemed a reason to stop treatment. The rate of treatment discontinuation has been reported to be 12.5% (Bissler 2013, Bissler 2015).

4 Effective from

June 2016

5 Evidence Summary

The main body of literature relating to everolimus (Votubia®) and tuberous sclerosis complex-associated renal angiomyolipoma comprises one double-blinded, placebo-controlled, international multi-centre randomised controlled trial (RCT) (Bissler, 2013), an unblinded, uncontrolled extension of this RCT (Bissler, 2015), and a subgroup analysis from an earlier RCT(Kingswood, 2014). No systematic reviews or meta-analyses relating to this treatment for AML were identified.

No specific published evidence exists relating to the use of the intervention in children. This is consistent with many other specialised interventions, due to the particular challenges in undertaking research in children, but it is biologically plausible to extrapolate the evidence garnered in adults to the paediatric age-range.

5.1 Efficacy

There is good evidence from one RCT (Bissler et al, 2013) which shows that for patients who have TSC-related AML, there is significant difference in AML response rate (50% reduction in AML volume in the absence of progression) between those who had everolimus (Votubia®) (42% (95%CI 31 to 53%) and those who were treated with placebo (0% (95%CI 0 to 9%)) ($p<0.0001$). The actual volume reduction of each group was not reported. It is not clear what the minimal volume reduction needs to be in order to achieve clinical significance in terms of avoidance of renal failure, acute haemorrhage or death.

At the point that the RCT reported outcomes (median exposure to everolimus (Votubia®) 38 weeks, placebo 34 weeks), no cases of haemorrhage, renal failure or AML related deaths had occurred in either the placebo or the everolimus (Votubia®) group. This first phase of the study was not long enough to demonstrate that beyond the 38 weeks, everolimus (Votubia®) will prevent any of these three events from occurring.

The study also reported that everolimus (Votubia®) has an effect over placebo on tumour progression which was observed in 4% (3/79 patients) vs 21% (8/39 patients). However, it is not clear that this, or the estimated progression free rates, are statistically significant due to missing confidence intervals or p-values.

There is no evidence which directly compares the clinical effectiveness of everolimus (Votubia®) for TSC-related AML with any other treatment, including other mTOR inhibitors and current treatment options including embolization, surgical resection or nephrectomy.

5.2 Time to onset of benefit

The EXIST-2 study authors reported the median time (for responders) for AML response to be 2.9 months (Bissler et al, 2013).

5.3 Duration of benefit relating to dose – response

The EXIST-1 study reports that AML response rates were 53.3% (16/30) and 0% (0/14) for everolimus (Votubia®) and placebo-treated patients, respectively. After 12, 24 and 48 weeks of treatment, the proportions of patients in the everolimus (Votubia®) arm with ≥ 50% reduction in the sum of volumes of target angiomyolipomata were 56.5, 78.3 and 80.0%, respectively. Greater percentages of everolimus treated patients had angiomyolipoma reductions ≥30% at these same time points (82.6, 100 and 100% versus 8.3, 18.2 and 16.7% for everolimus versus placebo, respectively) (Kingswood, 2014).

The AML response rate (50% reduction of total AML volume) in Exist 2 (Bissler et al, 2015) was 42% (33/79 participants, 95% CI =31 to 53%) after a median of 8.7 months treatment. This increased to 54% (60/112 participants, 95% CI = 44 to 63%) after median exposure to everolimus (Votubia®) of 28.9 months in the extension study. Tumour stabilisation was also analysed, with 38 patients (33.9%) demonstrating stable disease and 1 (0.9%) showing disease progression as best overall response (Bissler et al, 2015).

The EXIST-2 extension study (n=112) (Bissler et al, 2015) reports that the proportion of patients who achieve an AML tumour volume reduction of ≥ 50% increases over time, from 44.2 %(46/104 patients) after 12 weeks to 64.5% (49/76 patients) after 96 weeks (and 72% at 144 weeks). Only 76 out of the initial 112 patients had been exposed to everolimus (Votubia®) for 96 weeks and only 22/112 at 144 weeks. There is uncertainty about the reliability of the reported response rates over time as the confidence intervals were not reported and the cohort size decreases. No p-values were reported for the above outcomes and given the overlap in confidence intervals, it is likely that the increase in response rate is not statistically significant, although the effect appears to be sustained. The evidence supporting treatment beyond 38 weeks is based on a prospective uncontrolled study (Bissler et al, 2015).

The median treatment exposure in the EXIST-2 RCT was 37 weeks (Bissler et al, 2013). There is a wide range of exposure times to everolimus (Votubia®) for the patients included in the uncontrolled EXIST-2 long-arm extension (Bissler et al, 2015) where the median duration of everolimus (Votubia®) exposure was 28.9 (range 0.5-46.2) months) and the number of patients exposed to everolimus (Votubia®) beyond 22 months was very small

(only 23 at 24 months decreasing to less than 10 by 32 months), This, combined with the lack of any control group, means that the outcomes are less certain than those reported in the initial RCT.

The authors do report that there is an increase in AML response rate over time. Although the increase cannot be confirmed (due to missing statistical information) the AML response rates (which were significant over placebo at the end of the RCT) continue and appear to be sustained over time.

The median time to progression was not reached at median exposure of 28.9 months as only six out of the 112 patients experienced disease progression due to either increase in kidney size or increase in AML size. We do not know for how long these patients had been exposed to everolimus (Votubia®).

The EXIST-2 study, as reported within the follow-up paper, found that no patient taking everolimus (Votubia®) had experienced a renal bleed, however one patient on placebo did leading to nephrectomy (Bissler 2015).

There is weak evidence (from estimated progression free rates) which suggests that treatment with everolimus (Votubia ®) will result in a low proportion of patients having progressive AML. However the wide range of everolimus (Votubia®) exposure times, combined with no control group means that these results should be treated with caution.

There is no evidence to indicate that treatment can be withdrawn at any point without a risk of subsequent progression. Therefore, the evidence suggests that in practice treatment with everolimus (Votubia®) might be continued long term beyond 38 weeks until the patient becomes intolerant of therapy for any reason or the AML progresses despite therapy. However the rate of treatment discontinuation has been reported to be 12.5% (Bissler 2013, Bissler 2015).

5.4 Evidence of biological effective dose and impact by age group

No ideal dose was reported split by age groupings within the literature. Dose was adjusted during the EXIST-2 trial based on adverse effects and use of anti-epileptic drugs.

The forest plot reported in the EXIST-2 RCT indicated that there is no difference in the magnitude of treatment effect for renal AML response rate between adults aged under 30years old and adults aged over 30 years old, who met the recruitment criteria of EXIST 2. No children were included in the EXIST-2 RCT.

The EXIST-1 trial was an RCT that assessed the effect of everolimus on patients with TSC-associated subependymal giant cell astrocytoma (SEGA). A subgroup analysis was performed on patients who also had renal AML (37/44 children aged 3-17 years of whom 23 were on active treatment and 14 were taking placebo), and this trial was a precursor to the EXIST-2 trial. It is not possible to compare the outcomes for these children with the adults in EXIST-2 as the starting dose was different and the doses were adjusted to maintain pre-dose everolimus (Votubia®) concentrations between 5 and 15ng/mL.

5.5 Safety

Overall, there is a paucity of long-term data on the safety of everolimus (Votubia®) in patients with TSC-associated renal AML. Adverse effects (mostly minor) are common, though these seem to be well-managed by dose-adjustments. Most of the adverse effects observed in the trials summarised in this section are expected with everolimus (Votubia®) use. The most common adverse events were stomatitis, nasopharyngitis, acne-like skin lesions, headache, cough, and hypercholesterolaemia and were primarily grade 1−2 (Bissler et al, 2013).

5.6 Cost effectiveness

There were no studies evaluating the cost effectiveness of everolimus (Votubia®) for the treatment of renal angiomyolipoma associated with tuberous sclerosis. The literature search conducted as part of this policy identified two abstracts of cost-effectiveness studies; however the full papers could not be accessed.

6 Equality statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

7 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.

Each provider organisation treating children with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

8 Responsible CRG

Specialised Cancer Surgery CRG.

9 Date approved

June 2016

10 Policy review date

The policy statement will be revised during 2016/17 with the publication of a clinical commissioning policy.

11 Links to other Policies

This policy statement follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

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