Integrated Impact Assessment Report for Clinical Commissioning Policies

Policy Reference Number	E09X04		
Policy Title	Everolimus for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex		
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Section K - Activity Impact			
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)	
K1 Current Patient Population & Demography / Growth	K 1.1 What is the prevalence of the disease/condition?	K1. 1 The policy proposes to **routinely commission** everolimus (Votubia ®) for those with subependymal giant cell astrocytomas (SEGAs) associated with tuberous sclerosis complex (TSC). **TSC** is a rare genetic disorder that causes non-cancerous (benign) tumours to develop in various parts of the body. TSC could often remain undiagnosed if the patient does not develop symptoms, and as such, there is large variation in reported prevalence, as described in the policy proposition.[i] A study supported by the Committee for Medicinal Products for Human Use, estimates the prevalence of TSC in EU countries at up	

		to 1 in 10,000.[ii] Based on this, there could be up to 5,425 patients in England with TSC.[iii] Of those that have TSC, between 5% and 20% will develop **SEGAs**.[iv] Based on this, the number of people with SEGAs due to TSC in England is estimated at between 271 and 1085.[v]
	K1.2 What is the number of patients currently eligible for the treatment under the proposed policy?	K1.2 The population eligible for treatment would be patients with SEGAs associated with TSC who are not suitable for surgery.[vi] Out of the patient population that have SEGAs, 50% (or 136 to 542) may not be suitable for surgery.[vii] Of those not suitable, around 10 to 38 patients are clinically likely to commence treatment each year.[viii] The population eligible for the treatment is therefore estimated in the region of 10 to 38 in 2014/15.[ix] *Based on clinical judgement, the target population is expected to be closer to the lower bound than the upper bound, with a best estimate of around 17 patients per year. This is treated as a central scenario for estimates going forwards, with the upper and lower bounds comprising the overall range.*[x] Of the patients commencing treatment, 5% are likely to stop treatment due to adverse reaction, side-effects or developing resistance to the drug.[xi] As such, of the number of new patients eligible for starting the treatment each year, the number continuing with the treatment post

		year 1 is in the region of 9 to 36.[xii]
	K1.3 What age group is the treatment indicated for?	K1.3 The treatment is indicated for children and adults (all ages).
	K1.4 Describe the age distribution of the patient population taking up treatment?	K1.4 Based on data collected by the Tuberous Sclerosis Alliance, the age distribution for those with TSC ranges from 3 months to 81 years, and around 70% are children. [xiii] More specifically, the patient population taking up the treatment generally refers to children and young adults. This is because SEGAs usually develop during childhood and adolescence, and rarely develop in patients that have reached the age of 30. [xiv] The majority of SEGA cases are in patients aged 20 years or younger, although patients may present as late as 40.[xv]
	K1.5 What is the current activity associated with currently routinely commissioned care for this group?	K1.5 The number of **IFRs** considered by NHS England for individuals with the conditions listed within this policy was 8 in 2014/15 and 1 in the first half of 2015/16. [xvi] It was not possible to estimate the number of approved IFRs for everolimus. Patients treated with everolimus receive regular monitoring: the volume and size of the SEGA are evaluated with MRI scans every 6 months and the everolimus blood concentrations are regularly monitored to allow for dose titration.[xvii] The other pharmacological treatment for this group of patients may be

		'off-licence' rapamycin (sirolimus).[xviii] This may be prescribed in a similar way to everolimus and to both symptomatic and asymptomatic patients. It is not known how many patients receive rapamycin. Symptomatic patients, specifically those with acute symptoms who have large unresectable lesions, would likely require a **de-bulking procedure** to reduce the size of the SEGA. These patients may also receive **palliative shunt procedures**, specifically a ventriculoperitoneal shunt, to relieve the build-up of cerebrospinal fluid (CSF).[xix]
	K1.6 What is the projected growth of the disease/condition prevalence (prior to applying the new policy) in 2, 5, and 10 years?	K1.6 Diagnosis of TSC related SEGA depends on clinical features that are variable and the prevalence rate is increasing with better identification of less severe cases. The prevalence rate of this condition may increase in the future as the number of patients diagnosed with TSC increases. There is limited information to estimate this increase - see K2.2 for further details. As such, it is assumed that the **prevalent population for TSC** identified in K1.1 would grow in line with demographic growth. This is estimated to be in the region of :[xx] • ~5,500 in 2016/17 (year 1) • ~5,540 in 2017/18 (year 2) • ~5,660 in 2020/21 (year 5) • ~5,850 in 2020/21 (year 10) Amongst these, the number of patients in the **target population** as identified in K1.2 would increase cumulatively each year and is anticipated to be in the region of:[xxi] • ~ 10 to 39 in 2016/17 (year 1) • ~ 20 to 75 in 2017/18 (year 2) • ~ 51 to 195 in 2020/21 (year 5)

		• ~ 106 to 402 in 2025/26 (year 10)
	K1.7 What is the associated projected growth in activity (prior to applying the new policy) in 2, 5 and 10 years?	K1.7 In the absence of the proposed policy, it is assumed that the current levels of activity (identified in K1.5) will remain the steady state in future years. Based on this, there is expected to be some continued use of Everolimus for SEGA, but the levels are unknown (less than 8) as set out in K1.5. As there is evidence demonstrating that everolimus is clinically effective in reducing SEGA volume and thereby preventing symptoms such as hydrocephalus from developing in patients, with the policy in place it is expected that activity related to de-bulking and shunt procedures would decrease.[xxii]
	K1.8 How is the population currently distributed geographically?	K1.8 Across England - no differences in geographical distribution were identified.[xxiii]
K2 Future Patient Population & Demography	K2.1 Does the new policy: move to a non-routine commissioning position / substitute a currently routinely commissioned treatment / expand or restrict an existing treatment threshold / add an additional line / stage of treatment / other?	K2.1 The new policy would commission everolimus for those eligible (as described in K1.2) - previously everolimus (Votubia) was not routinely commissioned.
	K2.2 Please describe any factors likely to affect growth in the patient population for this intervention (e.g. increased disease prevalence, increased survival)	K2.2 Evolution in diagnostic testing over time has resulted in changes in the prevalence of TSC over time. Increased surveillance such as frequency of MRI scans has led to an increase in the number of those that are diagnosed with TSC and SEGAs.

		In recent years, there has been an increase in the number of prenatal and antenatal screenings for this condition.[xxiv] [xxv] If the rise in prenatal screenings were to continue, there could be a lower incidence of TSC in the population; and with more antenatal screenings, which lead to the earlier diagnosis of SEGAS, the numbers of those presenting with inoperable SEGAs could fall in the future.[xxvi] However, there is not sufficient information to quantify these changes.
	K 2.3 Are there likely to be changes in geography/demography of the patient population and would this impact on activity/outcomes? If yes, provide details	K2.3 None identified.
	K2.4 What is the resulting expected net increase or decrease in the number of patients who will access the treatment per year in year 2, 5 and 10?	K2.4 Under a routinely commissioned position, there would be a net increase in the number of patients receiving everolimus from the current levels as set out in K1.7. Currently, the number of patients accessing the treatment each year could not be confirmed and could be up to 8 as set out in K1.5. Under the policy, in the first year that the policy has effect, almost all patients that are clinically eligible (as identified in K1.2) are expected to begin treatment. Activity for everolimus is assumed to follow a phase-in of 75% in year 1, with the first full year effect in year 2. The **net increase** as compared to the do nothing scenario (assuming eight are receiving the drug in the do nothing scenario) in the overall size of the cohort of patients receiving the treatment is estimated to be: [xxvii] [xxviii] [xxix] • ~ 0 to 21 in 2016/17 (year 1, 75% effect)[xxx]

		• ~ 12 to 67 in 2017/18 (year 2) • ~ 43 to 187 in 2020/21 (year 5) • ~ 98 to 394 in 2025/26 (year 10) As patients are treated with everolimus long-term, once patients commence treatment they are expected to remain in the target population for the duration of the 10 year modelling horizon. Hence, the number of new patients accessing treatment is expected to grow cumulatively, increasing by the incident population each year.
K3 Activity	K3.1 What is the current annual activity for the target population covered under the new policy? Please provide details in accompanying excel sheet K3.2 What will be the new activity should the new / revised policy be implemented in the target population? Please provide details in accompanying excel sheet	K3.1 Current annual activity is identified in K1.5. K3.2 Under the policy, it is estimated that all of the eligible population would receive **everolimus**. The treatment would be long term and it is assumed that 5% of the patients would stop the treatment due to side effects, adverse reactions or developing resistance to the drug.[xxxi] There is not anticipated to be a significant backlog of patients; those who currently demonstrate exceptionality receive everolimus through IFRs and the cancer-drug fund.[xxxii] Patients that receive everolimus may discontinue with the 'off-licence' rapamycin.[xxxiii] Based on the evidence from studies[xxxiv] and discussions with the clinicians, the reduction in SEGA volume in patients may mean that there are:

		• more patients who have SEGAs that can be surgically removed • fewer patients who present with acute intracranial pressure and, hence fewer patients that require a palliative shunt procedure. However, while these effects may arise, at present the evidence was not sufficient to be able to quantify this.
	K3.3 What will be the comparative activity for the 'Next Best Alternative' or 'Do Nothing' comparator if policy is not adopted? Please details in accompanying excel sheet	K3.3 In the 'do nothing' scenario, the activity for everolimus in the target population would be the same as in K1.5 and K1.7. The patients who currently receive everolimus (up to 8 as discussed in K1.2) are expected to continue, whilst the patients who would have received everolimus under the policy are expected to be treated with either 'off-licence' rapamycin or no comparative medication. The majority of these patients are likely to develop symptomatic SEGAs. As set out in K1.7, the activity for de-bulking procedures and palliative shunts are expected to be greater in the 'do-nothing' than under the policy. In the absence of everolimus, patients would receive at least one de-bulking procedure and one palliative shunt. Clinical experience shows that c. 50% of patients would need a shunt revision. For patients who do not receive everolimus, and who are contraindicated to surgery, disease progression may lead to worsening symptoms of SEGA. These patients have a high risk of mortality.
K4 Existing Patient Pathway	K4.1 If there is a relevant currently routinely commissioned treatment, what	K4.1 Everolimus is not currently routinely commissioned. It is used in cases where patients are not amenable to surgery – the pathway prior

	is the current patient pathway? Describe or include a figure to outline associated activity	to that point is: 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. Some patients are not amenable to surgery due to difficulty of surgery, size of SEGA, multiple or infiltrative SEGA or surgery has already been performed and there is residual SEGA.
	K4.2. What are the current treatment access criteria?	K4.2 N/A – Everolimus is not currently routinely commissioned.
	K4.3 What are the current treatment stopping points?	K4.3 N/A – Everolimus is not currently routinely commissioned.
K5 Comparator (next best alternative treatment) Patient Pathway	K5.1 If there is a 'next best' alternative routinely commissioned treatment what is the current patient pathway? Describe or include a figure to outline associated activity.	K5.1 Alternative treatment strategies include incomplete resection and / or palliative surgery (diverting cerebro-spinal fluid by inserting a shunt). See K4.1 for patient pathway prior to this point.

	K5.2 Where there are different stopping points on the pathway please indicate how many patients out of the number starting the pathway would be expected to finish at each point (e.g. expected number dropping out due to side effects of drug, or number who don't continue to treatment after having test to determine likely success). If possible please indicate likely outcome for patient at each stopping point.	K5.2 Of those who have SEGAs, an estimated 50% may be inoperable.[xxxv]
K6 New Patient Pathway	K6.1 Describe or include a figure to outline associated activity with the patient pathway for the proposed new policy	K6.1 See K4.1 for initial diagnosis and surgical options. If a patient is not amenable to surgery, 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 (recommended at 4.5mg per m2 body surface area) 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.
	K6.2 Where there are different stopping points on the pathway please indicate how many patients out of the number starting the pathway would be expected to finish at each point (e.g. expected number dropping out due to side effects	K6.2 See K5.2, and stopping criteria: (i) Evidence of persistently high IGF-1 levels as assessed by blood tests; OR

	of drug, or number who don't continue to treatment after having test to determine likely success). If possible please indicate likely outcome for patient at each stopping point.	(ii) Evidence of persistently high GH concentrations as assessed by blood tests; OR (iii) Serious adverse effects; OR (iv) Non-compliance indicated by blood levels despite reasonable efforts to educate patients and/or secure regular drug administration.
K7 Treatment Setting	K7.1 How is this treatment delivered to the patient? o Acute Trust: Inpatient/Daycase/ Outpatient o Mental Health Provider: Inpatient /Outpatient o Community setting o Homecare delivery K7.2 Is there likely to be a change in delivery setting or capacity requirements, if so what? *e.g. service capacity*	K7.1 Everolimus is administered orally – and usually via homecare delivery arrangements.[xxxvi] K7.2 No change anticipated.
K8 Coding	K8.1 In which datasets (e.g. SUS/central data collections etc.) will activity related to the new patient pathway be recorded? K8.2 How will this activity related to the	K8.1 Everolimus is a high cost drug excluded from tariff, so it should be captured in the high cost drug dataset for routine commissioning – see K9.1. K8.2 Activity should be identified through the high cost drug dataset,

	new patient pathway be identified?(e.g. ICD10 codes/procedure codes)	by drug name and indication. A standard naming convention is recommended.
K9 Monitoring	K9.1 Do any new or revised requirements need to be included in the NHS Standard Contract Information Schedule? If so, these must be communicated to CTownley@nhs.net, ideally by end of October to inform following year's contract	K9.1 The Information Schedule should be updated to include a requirement for data to be collected in Blueteq.
	K9.2 If this treatment is a drug, what pharmacy monitoring is required?	K9.2 See K9.3.
	K9.3 What analytical information /monitoring/ reporting is required?	K9.3 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. 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).
	K9.4 What contract monitoring is required by supplier managers? What changes need to be in place?	K9.4 N/A

	K9.5 Is there inked information required to complete quality dashboards and if so is it being incorporated into routine performance monitoring?	K9.5 N/A
	K9.6 Are there any directly applicable NICE quality standards that need to be monitored in association with the new policy?	K9.6 None available.
	K9.7 Do you anticipate using Blueteq or other equivalent system to guide access to treatment? If so, please outline. *See also linked question in M1 below*	K9.7 Centres to use Blueteq to track and audit use of everolimus, in order to ensure it is administered according to the Criteria for Commissioning.
Section L - Service Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
L1 Service Organisation	L1.1 How is this service currently organised? (i.e. tertiary centres, networked provision)	L1.1 Tertiary centres
	L1.2 How will the proposed policy change the way the commissioned service is organised?	L1.2 No change, although the prescribing consultant should monitor trough levels of everolimus after initiation of treatment, dose changes, addition of concomitant medications or change in liver function. Additionally primary care services may be involved in performing some routine blood tests and treating any minor adverse events.

L2 Geography & Access	L2.1 Where do current referrals come from?	L2.1 Patients with TSC are monitored with annual multiphase MRI scans. If a SEGA lesion is detected, a multi-disciplinary team determines whether to continue to monitor the lesion through regular scans or perform surgery to remove the lesion.
	L2.2 Will the new policy change / restrict / expand the sources of referral?	L2.2 No change.
	L2.3 Is the new policy likely to improve equity of access	L2.3 No change.
	L2.4 Is the new policy likely to improve equality of access / outcomes?	L2.4 No change.
L3 Implementation	L3.1 Is there a lead in time required prior to implementation and if so when could implementation be achieved if the policy is agreed?	L3.1 Not applicable.
	L3.2 Is there a change in provider physical infrastructure required?	L3.2 No change required.
	L3.3 Is there a change in provider staffing required?	L3.3 No change required.

	L3.4 Are there new clinical dependency / adjacency requirements that would need to be in place?	L3.4 No change required.
	L3.5 Are there changes in the support services that need to be in place?	L3.5 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).
	L3.6 Is there a change in provider / inter-provider governance required? (e.g. ODN arrangements / prime contractor)	L3.6 No change required.
	L3.7 Is there likely to be either an increase or decrease in the number of commissioned providers?	L3.7 No change anticipated.
	L3.8 How will the revised provision be secured by NHS England as the responsible commissioner? (e.g. publication and notification of new policy, competitive selection process to secure revised provider configuration)	L3.8 Publication of new policy.
L4 Collaborative Commissioning	L4.1 Is this service currently subject to or planned for collaborative commissioning arrangements? (e.g. future CCG lead, devolved commissioning arrangements)?	L4.1 No

Section M - Finance Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
M1 Tariff	M1.1 Is this treatment paid under a national prices*, and if so which?	M1.1 The drug would be excluded from national prices as it is a high cost drug – see M1.2
	M1.2 Is this treatment excluded from national prices	M1.2 For non-chemotherapy indications, everolimus (Votubia®) is a high cost drug excluded from national tariff. [xxxvii]
	M1.3 Is this covered under a local price arrangements (if so state range), and if so are you confident that the costs are not also attributable to other clinical services?	M1.3 The drug is excluded from national prices. The net list price of everolimus (Votubia®) is (assuming a 30-day supply): - 10 mg 30-tab pack =£2970.00 - 5 mg 30-tab pack = £2250.00 - 2.5mg 30-tab pack =£1200.00 The patent for everolimus (Votubia®) is expected to expire in 2021.[xxxviii] A generic could enter the market soon after and this could lead to a price fall of 60% – 70%.[xxxix]
	M1.4 If a new price has been proposed how has this been derived / tested? How will we ensure that associated activity is not additionally / double charged through existing routes	M1.4 Not applicable.
	M1.5 is VAT payable (Y/N) and if so has it been included in the costings?	M1.5 VAT could be recoverable if homecare delivery arrangements are used.[xl]

	M1.6 Do you envisage a prior approval / funding authorisation being required to support implementation of the new policy?	M1.6 Not applicable.
M2 Average Cost per Patient	M2.1 What is the revenue cost per patient in year 1?	M2.1 The revenue cost per patient is dependent on the dosage that each patient in the target population receives and how this dosage is titrated over the course of the treatment. The recommended dosage is 4.5mg for each metre of body surface area in the patient[xli], although those aged 1-3 may receive a dosage of 7mg/m^2 .[xlii] As the drug will be prescribed to both young children and adults, the dosage is likely to vary considerably.[xliii] In year one the cost per patient per year is estimated at[xliv]: • £36,200 assuming a 10mg dosage • £27,400 assuming a 5mg dosage (this is considered for the cost estimates going forwards) • £14,600 assuming a 2.5mg dosage In addition, patients treated with everolimus receive regular monitoring of: 1) **SEGA size and growth**. This may cost £150-330 for each MRI scan[xlv] and with each patient receiving an MRI scan every 6 months[xlvi], this may cost £300-660p.a. 2) **Trough level monitoring of blood levels.** *Consultants prescribing Everolimus should monitor the drug's trough levels. Novartis is currently offering a free-of-charge trough level monitoring service through its funding of Analytical Services*

		International (ASI) Ltd. This cost saving has been omitted on the basis of uncertainty on how long the services will be funded by Novartis. The patent for Everolimus (Votubia®) SPC expires in July 2018 and generics may begin to enter the market in 2021. As a result, the price is likely to remain stable up until 2021, when the price of Everolimus is expected to fall by c.65%.[xlvii] From 2021 onwards the cost per patient for a 5mg dosage could be between £9,600 and £11,000.[xlviii]
	M2.2 What is the revenue cost per patient in future years (including follow up)?	M2.2 If the patient continues to be on the treatment, the revenue cost in future years would be the same as that in year 1 (as described in M2.1)
M3 Overall Cost Impact of this Policy to NHS England	M3.1 Indicate whether this is cost saving, neutral, or cost pressure to NHS England	M3.1 The adoption of this policy will result in a **net cost pressure**[xlix] to NHS England to the magnitude of[l]: • c. £135k in 2016/17 (assuming 75% phasing[li]) • c. £705k in 2017/18 • c. £760k in 2021/22[lii] • c. £1.65m in 2025/26 *There is significant uncertainty in the number of patients who may access the treatment as defined in K1.2. Please refer to M6.1 for a range.* However; a proportion of this cost pressure is likely to be **mitigated** through avoided need for palliative shunts/de-bulking. Due to the nature of the disease, the exact proportion is difficult to estimate (details below).

		Aside from the cost pressure described, there may be **cost savings** to NHS England from reducing the volume of SEGAs in patients.[liii] With the policy in place, and with more patients receiving everolimus activity for de-bulking and palliative shunt procedures may fall in future years, as outlined in K1.7 and K3.3. However, there is significant uncertainty around these estimates given the variation in treatment options and outcomes. For reference, the tariff for these procedures:[liv] − £3,120 for a elective shunt and £9,850 for a non-elective shunt[lv] [lvi] − £3,650 for a debulking procedure[lvii] [lviii] These costs are likely to be avoided when using everolimus. For example, *under the assumption that 50% of the patient group receives a replacement shunt procedure over the 5-year horizon and all patients receive one debulking procedure,* the total costs per year in the 'do-nothing' scenario (for the incident population) may approximately be c. £135k assuming all patients receive elective shunts procedures.[lix]
	M3.2 Where this has not been identified, set out the reasons why this cannot be measured	M3.2 Not applicable.
M4 Overall cost impact of this policy to the NHS as a whole	M4.1 Indicate whether this is cost saving, neutral, or cost saving for other parts of the NHS (e.g. providers, CCGs)	M4.1 Cost neutral. There may be minor cost savings to the CCGs as fewer patients are anticipated to develop the symptoms associated with increased cerebrospinal fluid pressure.[lx] These may include amongst others:

		nausea, vomiting, and seizures.[lxi] In response patients may receive short-term medical management with anti-diuretics and steroids prior to surgical intervention This activity is generally commissioned by CCGs, who are likely to experience cost savings from a reduction in this activity and more generally from less overall contact with the patient group. However these savings are likely to be very minor. This minor cost saving for CCGs may be offset to some degree by greater activity relating to the side-effects of everolimus. Whilst a small proportion may develop severe complications from the suppression of the immune system, a majority of patients may develop ulcerations. The cost of treating these conditions tend to be financed by CCGs, creating a minor cost pressure for CCGs who have everolimus patients under their remit.
	M4.2 Indicate whether this is cost saving, neutral, or cost pressure to the NHS as a whole	M4.2 As discussed in M3.1.
	M4.3 Where this has not been identified, set out the reasons why this cannot be measured	M4.3 Not applicable.
	M4.4 Are there likely to be any costs or savings for non NHS commissioners / public sector funders?	M4.4 There was not sufficient evidence to assess any indirect impacts of the intervention for the indication noted.

M5 Funding	M5.1 Where a cost pressure is indicated, state known source of funds for investment, where identified *e.g. decommissioning less clinically or cost-effective services*	M5.1 To be discussed at CPAG.
M6 Financial Risks Associated with Implementing this Policy	M6.1 What are the material financial risks to implementing this policy?	M6.1 There is significant uncertainty in the number of patients who will access the treatment – given the wide range in the number of clinically eligible patients. As such, the lower and upper estimates around the cost pressure identified above is estimated to be in the region of: • £10k to £575k in 2016/17[lxii] • £325k to £1.8m in 2017/18 • £415k to £1.8m in 2020/21 • £0.9m to £3.8m in 2025/26 Further, currently, the IA captures only the financial impacts from the drug and does not consider the potential cost savings from the clinical effectiveness of the treatment. This might be overstating the overall cost pressure.
	M6.2 Can these be mitigated, if so how?	M6.2 Blueteq could be used to ensure everolimus is used at the correct point in the pathway, and trend analysis could be used to assess whether the correct questions are being asked to ensure proper use within the policy.
	M6.3 What scenarios (differential	M6.3 The range of cost pressure set out in M3.2 is based on three

	assumptions) have been explicitly tested to generate best case, worst case and most likely total cost scenarios?	scenarios developed around the risks of the target population size. The cost of the everolimus is assumed to be £27,400 per patient per year. [lxiii] In addition, 5% of patients are expected to discontinue treatment with everolimus each year, as set out in K1.2. The high scenario is based on a high prevalence of TSC in the population and therefore a high number of individuals (38) in the eligible population. A low scenario is estimated based on a lower prevalence of TSC and fewer patients in the eligible population (10). A mid scenario assumes a target population of 17 patients. Based on clinical judgement, the mid-point (24) may not be appropriate as there is a greater probability that the target population may be closer to 10 than 28.[lxiv] Further, the net financial impact estimates in year 1 assumes that all 8 IFR applications for the drug (and this indication) were approved – and hence is part of the baseline expenditure. If none were approved – then the additional costs from these patients could be c.£200k upto the patent expiry dates and c.£75k thereafter.
M7 Value for Money	M7.1 What evidence is available that the treatment is cost effective? *e.g. NICE appraisal, clinical trials or peer reviewed literature* M7.2 What issues or risks are associated	M7.1 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. M7.2 Not applicable.

	with this assessment? *e.g. quality or availability of evidence*	
M8 Cost Profile	M8.1 Are there non-recurrent capital or revenue costs associated with this policy? *e.g. Transitional costs, periodical costs* M8.2 If so, confirm the source of funds to meet these costs	M8.1 None identified. M8.2 Not applicable.

[i] The estimated the prevalence of the condition in the UK ranges between 8.8 per 100,000 (O'Callaghan FJ: Tuberous sclerosis. BMJ Clinical Research 318(7190):1019-20 · May 1999; Accessed via: https://www.researchgate.net/publication/13093344_Tuberous_sclerosis) and 1 in 8,000 (Consultation on the UK Plan for Rare Diseases – Tuberous Sclerosis Complex, Tuberous Sclerosis Association, 2012).

[ii] European Medicines Agency 2011, see policy proposition. Recommendation for maintenance of orphan designation at the time of marketing authorisation: Votubia (everolimus) for the treatment of tuberous sclerosis. Accessed online via: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_review/2011/10/WC500116142.pdf

[iii] This applies the prevalence rates to ONS (2012) population projections for 2014/15.

[iv] Campen, C. and Porter, B. (2011). Subependymal Giant Cell Astrocytoma (SEGA) Treatment Update. Curr Treat Options Neurol, 13(4), pp.380-385. Accessed online via: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3130084/

[v] This applies the prevalence rates to ONS (2012) population projections for 2014/15.

[vi] See policy proposition

[vii] Based on discussions with the policy working group.

[viii] Based on discussions with the policy working group – see policy proposition.

[ix] Around 10% of the target population are expected to be between the age of 1 and 3. This age group are expected to receive a higher dosage (7mg/m^2) compared to older patients (4.5mg/m^2)

[x] Based on discussions with the policy working group

[xi] See policy proposition

[xii] After applying the 5% drop-out assumption to the target population of 10-38.

[xiii] http://www.tsalliance.org/pages.aspx?content=560

[xiv] Franz DN. Pharmacologic Management of Tuberous Sclerosis Complex- associated Subependymal Giant Cell Astrocytomas. Expert Opinion on Orphan Drugs. 2014;2(1):53-66

[xv] Based on discussion with the policy working group - evidence from clinical practice.

[xvi] Based on IFR data for NHS England in 2014/15, including both paediatric and adult IFRs.

[xvii] Votubia.com, (2016). Dosing and Administration of VOTUBIA® (everolimus) for Healthcare Professionals in the EU. [online] Available at: http://www.votubia.com/dosing-and-administration.jsp [Accessed 30 Jan. 2016].

[xviii] Based on discussions with the policy working group.

[xix] Based on discussions with the policy walking group.

[xx] The demographic specific growth rate is estimated using the cohorts from the ONS (2012) population projections to calculate a growth rate of the population of England over the period 2015 to 2025. Rounded to the nearest five.

[xxi] Assuming that 95% of patients who start treatment each year continue whilst 5% of patients stop treatment each year.

[xxii] Based on discussions with the policy working group.

[xxiii] Patients may, however, decide to locate closer to the centres of excellence.

[xxiv] Hope Northrup, MD, FACMG, Mary Kay Koenig, MD, Deborah A Pearson, PhD, and Kit-Sing Au, PhD. Accessed via: http://www.ncbi.nlm.nih.gov/books/NBK1220/

[xxv] Whilst c.75% of new diagnosis are from new mutations developing in childhood and young adulthood, around 25% of new diagnosis may familial, identified through prenatal early diagnosis.

[xxvi] Based on discussions with the policy working group - with earlier diagnosis, fewer SEGAs may reach the volume and size at which they become inoperable.

[xxvii] Clinically eligible population growing in line with demographic growth.

[xxviii] Assuming that 5% of the eligible population stop treatment each year – the drop-out rate assumed in this impact assessment. .

[xxix] With the exception of year 1, these estimates are annualised.

[xxx] A 75% phasing is assumed for year 1 based on discussions with the policy working group.

[xxxi] The clinical trials suggest that this proportion would be small; in the trials between 0-5 percent of patients were discontinued from the treatment. In the Franz et al (2013) study there were no adverse events that led to discontinuation of the trial. In the Franz et al (2014) study, around 5% of patients were discontinued.

[xxxii] Based on discussions with the policy working group.

[xxxiii] This is because rapamycin and everolimus are both mTOr inhibtors. 'The mechanisms of action for sirolimus and other rapalogs (i.e. everolimus, temsirolimus, and ridaforolimus) are similar.' Curatolo, P. and Moavero, R. (2012). mTOR Inhibitors in Tuberous Sclerosis Complex. Current Neuropharmacology, 10(4), pp.404-415.

[xxxiv] The NHSE rapid evidence review found one relevant RCT (EXIST-1); this study found that everolimus was effective in reducing SEGA volume in a third of patients in the trial. 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.

[xxxv] Based on discussions with the Policy Working Group

[xxxvi] NICE, "everolimus for the second-line treatment of advanced renal cell carcinoma", NICE technology appraisal guidance [TA219], Published date: April 2011, accessed via https://www.nice.org.uk/guidance/ta219/chapter/2-The-technology, last accessed: 03/12/2015.

[xxxvii] Annex 7B. High cost drugs, devices and listed procedures. 2014-15 tariff - detailed high cost drugs.

[xxxviii] The patent expiry for the everolimus molecule is expected mid July 2018. However, Novartis has been granted for VOTUBIA, by European Medicines Agency (EMA), orphan drug exclusivity on the AML/SEGA indications until September 2021 (10 years from first approval obtained in September 2011). The EMA grant this incentive to encourage the development of medicines for rare disease in areas of high unmet need. However it is presently unclear whether Novartis will be able to maintain the VOTUBIA orphan drug exclusivity in the context of the commercialisation of generics of AFINITOR in the UK after July 2018.

[xxxix] Based on discussions with pharmacy lead. The modelling assumes a 65% reduction in the price of everolimus in 2020/21.

[xl] Section 3.2, When can goods being provided on prescription be zero-rated for VAT purposes? : https://www.gov.uk/government/publications/vat-notice-70157-health-professionals-and-pharmaceutical-products/vat-notice-70157-health-professionals-and-pharmaceutical-products

[xli] NHSE rapid evidence review. Confirmed by discussion with the clinician.

[xlii] Approximately 10% of the target population are aged 1-3 and may therefore require this dosage.

[xliii]The 5mg dose would be for a typical 9 year old with $1m^2$ surface area. An adult would likely have double this dose, 10mg.

[xliv] Rounded to nearest hundred.

[xlv] After applying a MFF uplift of 10% to the tariff for MRI scan of £138 to £299 (the cost depends on the number of areas). 2014-15 tariff - admitted patient care & outpatient procedures.

[xlvi] Based on discussions with the policy working group.

[xlvii] This information was gathered from discussions with the everolimus for AML clinical and policy working group.

[xlviii] The range is based on a 60-70% reduction in price as set out in M3.1.

[xlix] Compared to the do nothing scenario where up to 8 patients may be receiving IFR. See M6.3 for further details.

[l] Rounded to the nearest ten thousand

[li] Based on discussions with policy working group

[lii] As noted in M2.1, generics may enter the market from year 5 leading to a price drop of c.65%

[liii] Data from the Phase I–II study (C2485) indicated that everolimus therapy was associated with marked reduction in the volume of SEGAs and seizure frequency.

[liv] All paediatric neurosurgery is commissioned by NHS England [E09 – Paediatric Neurosciences] under the 119. Specialist neuroscience services for children and young people service. NHS England. Manual for prescribed specialised services 2013/14.

[lv] Based on the tariff for the HRG code – AA14 A-B 'Intracranial Procedures ' – identified through the corresponding OPCS code - A124 'Creation of ventriculoperitoneal shunt' – listed in the Code to Grouper document.

[lvi] A MFF uplift of 10% has been applied to the elective tariff cost of £2,840 and to the non-elective cost of £8,957. Annex 5A National prices (2014/15).

[lvii] Based on the tariff for the HRG code - AA09 'Intracranial Procedures Except Trauma with Other Diagnoses - category 4 with CC' - Identified through searching the OPCS code - A025 'Excision of lesion of tissue of cerebellum'.

[lviii] A MFF uplift of 10% has been applied to the elective tariff cost of £3,317. Annex 5A National prices (2014/15).

[lix] These estimates refer to the mid scenario. Costs may be higher if patients were to receive emergency shunts at c. £300k.

[lx] Based on discussions with the policy working group.

[lxi] Tsalliance.org, (2016). *SEGA or SGCT*. [online] Available at: http://www.tsalliance.org/pages.aspx?content=602 [Accessed 29 Jan. 2016].

[lxii] Assuming 75% phasing (100% phasing from year 2 onwards). Based on discussions with the policy working group.

[lxiii] This is the cost associated with a dosage of 5mg per day.

[lxiv] Based on discussions with the policy working group.