Integrated Impact Assessment Report for Clinical Commissioning Policies			
Policy Reference Number	ID001		
Policy Title	Everolimus as adjunctive treatment for partial-onset seizures in children and adults with tuberous sclerosis complex. Proposal **for routine commission** (ref A3.1)		
Lead Commissioner	Penelope Gray	**Clinical Lead**	Finbar O'Callaghan
Finance Lead	Jazz Nandra	**Analytical Lead**	Click here to enter text.

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About this Impact Assessment: instructions for completion and explanatory notes
• Each section is divided into themes. • Each theme sets out a number of questions. • All questions are answered by selecting a drop down option or including free text. • Free text boxes are provided to enable succinct relevant commentary to be added which explains the rationale for response or assumption. Please limit responses to 3 sentences of explanatory text. • Data in this document is either drawn from one of the relevant policy documents or a source for the information is provided. • Where assumptions are included where data is not available, this is specified.

Section A - Activity Impact	
A1 Current Patient Population & Demography / Growth	
A1.1 Prevalence of the disease/condition.	Around 10 in 100,000 people have tuberous sclerosis complex (TSC). This represents 0.01% of the population. Based on this, there could be up to 5,500 people in England with TSC. (Committee for Medicinal Products for Human Use, European Medicines Agency, 2011). However, this is likely to be an underestimation of the true prevalence, because prevalence is increasing with better identification of less severe cases. *Source: Policy Proposition section 6; clinical expert opinion at policy working group.*
A1.2 Number of patients currently eligible for the treatment according to the proposed policy commissioning criteria.	Of those that have TSC, around 84% have TSC associated seizures. There are approximately 4,600 TSC-associated epilepsy patients in England. The proportion of people with TSC-related refractory epilepsy varies depending on the evidence source between 36% (Kingswood et al., 2017) and 63% (Chu-Shore et al., 2010). After discussion with clinical experts a mid-point of this range of 50% was agreed. Using this data, the resource impact estimates the number of people with TSC-related refractory epilepsy in England to be around 2,300 people (row 30

<table>
<tr><td></td><td>‘Assumptions input’ worksheet – resource impact template). This figure is consistent with the mid-point of the range given in the DPP (1,500 and 3,000 people).
Source: Policy Proposition section 6; clinical expert opinion at policy working group.

Please note, 2,297 people are currently eligible for any treatment regimen. These people may go on to receive AEDs or receive other combination treatments in addition to AEDs. Therefore the number of treatments is going to be higher because some people have both AEDs and other therapies. These numbers are analysed in A3.2 below and reflected in the resource impact template (current practice and future practice assumptions – ‘Assumptions input sheet’).</td></tr>
<tr><td>A1.3 Age group for which the treatment is proposed according to the policy commissioning criteria.</td><td><u>Children and young people (from age 2 to 19) and adults over 19</u>
The treatment is indicated for children and young people aged 2 to 19 and adults (all ages).</td></tr>
<tr><td>A1.4 Age distribution of the patient population eligible according to the proposed policy commissioning criteria</td><td>It is currently estimated that around 29% of the people eligible for treatment are children and young people aged 2 to 19 years old, and 71% are adults aged over 19. TSC affects 1 in every 6,000 new born babies, therefore this estimate is likely to change over time. Using population growth estimates from the ONS, and applying the proposed commissioning criteria (see A1.2 above) included in the resource impact template, the age distribution of the eligible population in years 1,2,5 and 10 is:
<table>
<tr><th>Year</th><th>People aged 2-19 % eligible</th><th>People aged over 19 % eligible</th><th>Total</th></tr>
<tr><td>1</td><td>575</td><td>1,779</td><td>2,354</td></tr>
<tr><td>2</td><td>621</td><td>1,792</td><td>2,413</td></tr>
<tr><td>5</td><td>760</td><td>1,829</td><td>2,589</td></tr>
</table></td></tr>
</table>

	10 | 989 | 1,891 | 2,880 Source: Live births data - Office for National Statistics (2016); Incidence data -Epilepsy research UK (2015) 1 in 6,000 new born babies are born with TSC available from: https://www.epilepsyresearch.org.uk/extensive-epilepsy-surgery-can-benefit-tuberous-sclero Population projections used in resource impact template: ONS (2016)
A1.5 How is the population currently distributed geographically?	**Evenly** If unevenly, estimate regional distribution by %: North: enter % Midlands & East: enter % London: enter % South: enter % *Source:* Please specify Across England, no differences in geographical distribution are identified. People may choose to locate closer to specialist services.
A2 Future Patient Population & Demography	
A2.1 Projected changes in the disease/condition epidemiology, such as incidence or prevalence (prior to applying the new policy) in 2, 5, and 10 years?	**Other - detail below** The prevalence of 10 in 100,000 people and the incidence of 1 in 6,000 new-born babies is used to estimate projected changes in the disease epidemiology. Applying this assumption to the prevalence of TSC and ONS projected

<table>
<tr><td></td><td>population data, gives a growth in population numbers of:

5,600 in 2019/20 (year 2)
6,100 in 2022/23 (year 5)
6,700 in 2027/28 (year 10)
See row 15 of the Assumptions input worksheet from the Resource Impact Template.</td></tr>
<tr><td>A2.2 Are there likely to be changes in demography of the patient population and would this impact on activity/outcomes?</td><td><u>No</u></td></tr>
<tr><td>A2.3 Expected net increase or decrease in the number of patients who will be eligible for treatment, according to the proposed policy commissioning criteria, per year in years 2-5 and 10?</td><td>
<table>
<tr><td></td><td>Increase
People 2-19</td><td>Increase people aged over 19</td></tr>
<tr><td>Year 2</td><td>+92</td><td>+24</td></tr>
<tr><td>Year 3</td><td>+138</td><td>+36</td></tr>
<tr><td>Year 4</td><td>+185</td><td>+49</td></tr>
<tr><td>Year 5</td><td>+231</td><td>+61</td></tr>
<tr><td>Year 10</td><td>+460</td><td>+124</td></tr>
</table>
Source:
Resource impact template using epidemiology and incidence data applied to ONS population projections for each age group. These figures were calculated by subtracting year data in row 26 (people ages 2 to 19) and row 27 (people</td></tr>
</table>

	over 19) from year 0 (baseline). Note: The increase in people aged from 2 to 19 is higher year on year than the increase in people aged over 19 because the 2 to 19 age group takes into account incident cases from new born babies who become eligible for treatment from aged 2.
A3 Activity	
A3.1 What is the purpose of new policy?	**<u>Confirm routine commissioning position of an additional new treatment</u>** The purpose of the new policy is to commission everolimus for people eligible for treatment as described in A1.1 above. Standard of care is AEDs which offer symptomatic treatment. The policy proposes to add Everolimus to current treatments. This because Everolimus is a disease modifying drug in TSC that targets the mammalian target of rapamycin (mTOR) pathway. It works by blocking the over-activation of mTOR (a major cell growth and proliferation controller), which is thought to be the cause of seizures in people with TSC.
A3.2 What is the annual activity associated with the existing pathway for the eligible population?	Of the 2,300 people eligible for treatment (see A1.4 above) around 95% (2,200) of adults and children receive anti-epileptic drugs (AEDs). In addition to AEDs, some people may require other combination therapies, this is estimated to be around 15% (340) of the people eligible for treatment. **The estimated total number of treatments given for refractory TSC (either AEDs or AEDs in combination with other therapies) is therefore 2,500 treatments (at year 0 – this is located at cell G40 in the 'Assumptions input' worksheet of the resource impact template)** *Source:* Clinical opinion from policy working group 07/09/2017. Standard treatment is AEDs with a small percentage of people also receiving other options. Standard of care will vary as treatment is tailored to individual patient's clinical circumstances. It could include surgery, alternative AED combinations, vagus

<table>
<tr><td></td><td>nerve stimulation or ketogenic diet.</td></tr>
<tr><td>A3.3 What is the estimated annual activity associated with the proposed policy proposition pathway for the eligible population?</td><td>
<table>
<tr><th>Year</th><th>People aged 2 to 19</th><th>People aged 19 and over</th><th>Total</th></tr>
<tr><td>1</td><td>185</td><td>601</td><td>786</td></tr>
<tr><td>2</td><td>257</td><td>807</td><td>1,064</td></tr>
<tr><td>5</td><td>303</td><td>737</td><td>1,040</td></tr>
<tr><td>10</td><td>439</td><td>651</td><td>1,091</td></tr>
</table>
The figures above take into account people who are awaiting treatment with everolimus, therefore an initial uptake in year 1 of 40% is assumed.
This increases to 60% in year 2, and is estimated to achieve 75% uptake form year 3 onwards.
Source: Calculations from resource impact template (rows 54-56 of assumptions page) using epidemiology and target population data, and people stopping treatment. The uptake is profiled according to uptake estimates from PWG meeting 07.09.2017.
There is uncertainty around the number of people who receive treatment as this depends on a number of factors which include clinical manifestation of the persons TSC, age, treatment history and clinical experience. The numbers shown above are therefore based on published data where possible, supported by clinical knowledge and experience.</td></tr>
<tr><td>A3.4 What is the estimated annual activity associated with the next best alternative comparator pathway for the eligible population? If the only alternative is the existing pathway, please state ‘not applicable’ and move to A4.</td><td>Not applicable</td></tr>
<tr><td colspan="2">A4 Existing Patient Pathway</td></tr>
</table>

A4.1 **Existing pathway:** Describe the relevant currently routinely commissioned: • Treatment or intervention • Patient pathway • Eligibility and/or uptake estimates.	For people with TSC-related seizures, anti-seizure medication (known as anti-epileptic drugs or AEDs) is the standard treatment. For an AED to be considered appropriate it must have previously been shown to be effective for the patient's epilepsy and seizure type. For people whose TSC-related seizures have not adequately responded to treatment with at least 2 different AEDs given at therapeutic doses, other treatment options are available. This includes: • the additional use of 1 or more AED added on to their currently prescribed AED or the use of a different AED which has not been previously prescribed; and • the following treatments: ○ a ketogenic diet (a diet low in carbohydrates) usually for infants and young children (because it is difficult for adolescents and adults to remain on a strict diet); and/or ○ vagus nerve stimulation (a device which stops seizures by sending regular, mild pulses of electrical energy to the brain and is implanted under the skin in the chest and connected to the vagus nerve, which is the main nerve that connects the brain to the heart, lungs, upper digestive tract, and other organs of the chest and abdomen); and/or ○ surgical resection (surgical resection may not be suitable for everyone with TSC-related seizures that have not adequately responded to treatment with at least 2 different AEDs given at therapeutic doses. This is because many patients with TSC-related seizures will not have a single type of seizure which is clearly related to one location in the brain that can safely be removed. In addition, some patients choose not to undergo surgery. However, children with TSC-related refractory seizures should be assessed for surgical resection in accordance with

	NHS England's Children's Epilepsy Surgery Service Specification, November 2016 [Ref: E09/S/e]). **Pathway:** Once it is confirmed a person has a definite diagnosis of TSC, if the person has TSC-related seizures, the person will then be prescribed an anti-epileptic drug by a paediatric or adult neurologist, depending on the age of the person. First line treatments for focal seizures are: • Ages < 1 year: Vigabatrin • Ages > 1 year: Other GABAergic inhibitor as monotherapy (topiramate or carbamazepine) Second line treatments for focal seizures are: • Surgical resection of epileptogenic foci or tubers • Combination AEDs People who are medically refractory to first and second line treatments: • Other AEDs used in focal seizures • Vagus nerve stimulation (also receive this in addition to AEDs) • Ketogenic diet (also receive this in addition to AEDs) *Source:* Policy proposition – summary ;NICE 2012; Curatolo et al. 2012; Wheless et al. 2007; *The role of mTOR inhibition in the therapeutic algorithm of TSC-associated epilepsy was noted as an unanswered question in the clinical recommendations of the TSC Consensus Meeting for SEGA and Epilepsy Management. **Eligibility and uptake estimates** Of the 2,300 people eligible for treatment (see A1.2 above) around 95% (2,200) of adults and children receive anti-epileptic drugs (AEDs). In addition to AEDs, some people may require other combination therapies, this is estimated to be around 15% (340) of the people eligible for treatment. **The estimated total number of treatments given for refractory TSC (either AEDs or AEDs in combination with other therapies) is therefore 2,500 treatments (per year 0, row 40 'Assumptions input' worksheet – resource**

	impact template)
A4.2. What are the current treatment access and stopping criteria?	In England there are currently specialised commissioning policies recommending routine commissioning of everolimus for the treatment of Angiomyolipomas (AML) associated with TSC and SEGA associated with TSC. Data from NHS England indicates a very small number of people who have TSC and refractory seizures without AML or SEGA currently receive everolimus. Commissioning everolimus would mean that all eligible people in need of further medical treatment for TSC related refractory partial onset seizures would have access to the treatment regardless of any other manifestations of TSC. Treatment continues as long as clinical benefit is observed or until unacceptable toxicity occurs (company submission). *Source: NHSE Clinical commissioning policy: Everolimus for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex Ref: 16066/P.*
A4.3 What percentage of the total eligible population is expected to: a) Be clinically assessed for treatment b) Be considered to meet an exclusion criteria following assessment c) Choose to initiate treatment d) Comply with treatment e) Complete treatment?	a) 100% (0.010% general population & 0.017% of new born babies, this is used to calculate incidence of TSC in children and young people aged from 2 years to 19 years who are diagnosed at birth and go onto receive a treatment from aged 2 years.) b) 84% of people who have TSC associated seizures and 50% of these people who will be refractory to treatment c) 100% refractory and choose further treatment d) 100% e) 100%.

	Source: Per A1.2 above *& policy working group opinion.*
A5 Comparator (next best alternative treatment) Patient Pathway (NB: comparator/next best alternative does not refer to current pathway but to an alternative option)	
A5.1 **Next best comparator**: Is there another 'next best' alternative treatment which is a relevant comparator? *If yes, describe relevant* • *Treatment or intervention* • *Patient pathway* • *Actual or estimated eligibility and uptake*	**No**
A5.2 What percentage of the total eligible population is estimated to: a) Be clinically assessed for treatment b) Be considered to meet an exclusion criteria following assessment c) Choose to initiate treatment d) Comply with treatment e) Complete treatment?	N/A
A6 New Patient Pathway	
A6.1 What percentage of the total eligible population is expected to: a) Be clinically assessed for treatment b) Be considered to meet an exclusion criteria following assessment	a) 100% b) 84% of people who have TSC associated seizures and 50% of these people who will be refractory to treatment

c) Choose to initiate treatment d) Comply with treatment e) Complete treatment?	c) 75% d) 100% e) 83.4% *Source:* Please see A1.2 and A3.3 above. All people are estimated to comply with treatment because it is a once daily oral tablet. The percentage of people completing treatment with everolimus takes into account an annual discontinuation rate of 16.57% confirmed by the company.
A6.2 Specify the nature and duration of the proposed new treatment or intervention.	**Life long** Treatment is given as long as clinical benefit is observed. Unpublished clinical effectiveness evidence indicates long-term exposure to everolimus achieved sustained reductions in TSC – associated treatment-refractory seizures over time with adjunctive everolimus. *Source: Company submission Table 7 – POSTER Presented at the American Academy of Neurology (AAN) 2017 Annual Meeting; April 22-28, Boston MA. Sustained seizure reduction with adjunctive everolimus for treatment-refractory seizures associated with TSC: Long-term results from the phase 3 EXIST study. David N Franz et al.*
A7 Treatment Setting	
A7.1 How is this treatment delivered to the patient?	*Select all that apply:* Emergency/Urgent care attendance ☐ Acute Trust: inpatient ☐ Acute Trust: day patient ☐ Acute Trust: outpatient ☐ Mental Health provider: inpatient ☐

	<table><tr><td>Mental Health provider: outpatient</td><td>☐</td></tr><tr><td>Community setting</td><td>☐</td></tr><tr><td>Homecare</td><td>☐</td></tr><tr><td>Other</td><td>☒</td></tr></table> Please specify: Tertiary centre. The prescribing consultant will need to monitor trough levels of everolimus after initiation of treatment, dose changes, and addition of concomitant medications or liver function. For children, services will be provided through existing tertiary paediatric neuroscience centres. For adults, services will be provided through existing adult neurology centres.
A7.2 What is the current number of contracted providers for the eligible population by region?	<table><tr><td></td><td>PAEDIATRIC</td><td>ADULT</td></tr><tr><td>NORTH</td><td>5</td><td>8</td></tr><tr><td>MIDLANDS & EAST</td><td>3</td><td>5</td></tr><tr><td>LONDON</td><td>4</td><td>7</td></tr><tr><td>SOUTH</td><td>3</td><td>5</td></tr></table> Source: Info from NHSE – tertiary neurology centres.
A7.3 Does the proposition require a change of delivery setting or capacity requirements?	**No**
A8 Coding	

A8.1 Specify the datasets used to record the new patient pathway activity.

*expected to be populated for all commissioned activity

Select all that apply:

Aggregate Contract Monitoring *	☐
Patient level contract monitoring	☐
Patient level drugs dataset	☐
Patient level devices dataset	☐
Devices supply chain reconciliation dataset	☐
Secondary Usage Service (SUS+)	☐
Mental Health Services DataSet (MHSDS)	☐
National Return**	☐
Clinical Database**	☒
Other**	☐

**If National Return, Clinical database or other selected, please specify:
Everolimus is a high cost drug excluded from tariff. Activity could therefore be captured in the high cost drug dataset for routine commissioning. A requirement for data to be collected via Blueteq could also be introduced.

A8.2 Specify how the activity related to the new patient pathway will be identified.

Select all that apply:

OPCS v4.8	☐
ICD10	☒
Treatment function code	☐
Main Speciality code	☐
HRG	☐
SNOMED	☒

	Clinical coding / terming methodology used by clinical profession ☒ Everolimus for SEGA associated TSC is currently recorded on the Patient level drug dataset specification NHSE. UK data for healthcare resource utilisation uses data from Clinical Practice Research Datalink (CPRD) linked to the Hospital Episode Statistics (HES) database. It is assumed activity related to the new patient pathway would be identified using these data.
A8.3 **Identification Rules for Drugs:** How are drug costs captured?	**Already specified in current NHS England Drugs List document** Everolimus is already used for SEGAs associated TSC that are not amenable to surgery. Costs could be identified through the high cost drug dataset. If the drug has NOT already been specified in the current NHS England Drug List please give details of action required and confirm that this has been discussed with the pharmacy lead: Not applicable
A8.4 **Identification Rules for Devices:** How are device costs captured?	**Not applicable** .
A8.5 **Identification Rules for Activity:** How are activity costs captured?	**Already correctly captured by an existing specialised service line (NCBPS code within the PSS Tool)** If activity costs are already captured please specify the specialised service code and description (e.g. NCBPS01C Chemotherapy). NCBPS23M Paediatric Neurology NCBPS08O Adult Neurology

<table>
<tr><th colspan="2">A9 Monitoring</th></tr>
<tr><td>A9.1 Contracts
Specify any new or revised data flow or data collection requirements, needed for inclusion in the NHS Standard Contract Information Schedule.</td><td><u>None</u></td></tr>
<tr><td>A9.2 Excluded Drugs and Devices (not covered by the Zero Cost Model)
For treatments which are tariff excluded drugs or devices not covered by the Zero Cost Model, specify the pharmacy or device monitoring required, for example reporting or use of prior approval systems.</td><td>Select all that apply:
<table><tr><td>Drugs or Device MDS</td><td>☐</td></tr><tr><td>Blueteq</td><td>☒</td></tr><tr><td>Other prior approval</td><td>☐</td></tr></table>Please specify: NHSE could add a requirement for data to be collected via Blueteq</td></tr>
<tr><td>A9.3 Business intelligence
Is there potential for duplicate reporting?</td><td><u>No</u></td></tr>
<tr><td>A9.4 Contract monitoring
Is this part of routine contract monitoring?</td><td><u>No</u>
If yes, please specify contract monitoring requirement:
Click here to enter text.</td></tr>
<tr><td>A9.5 Dashboard reporting
Specify whether a dashboard exists for the proposed intervention?</td><td><u>No</u>

If no, will one be developed?
Not applicable</td></tr>
<tr><td>A9.6 NICE reporting</td><td><u>Yes</u></td></tr>
</table>

Are there any directly applicable NICE or equivalent quality standards which need to be monitored in association with the new policy?	If yes, specify how performance monitoring data will be used for this purpose. https://www.nice.org.uk/guidance/qs27 This quality standard includes a focus on tailoring treatment to the individual circumstances and needs of children and young people with epilepsy so that they are offered the most suitable treatment.
Section B - Service Impact	
B1 Service Organisation	
B1.1 Describe how the service is currently organised? (i.e. tertiary centres, networked provision etc.)	Current services are delivered by existing tertiary paediatric neuroscience centres. For adults, services are delivered by tertiary adult neurology centres. *Source:* NHSE
B1.2 Will the proposition change the way the commissioned service is organised?	**No**
B1.3 Will the proposition require a new approach to the organisation of care?	**No change to delivery of care**
B2 Geography & Access	
B2.1 Where do current referrals come from?	*Select all that apply:* GP ☒ Secondary care ☒ Tertiary care ☐

	Other ☒ Please specify: Other = Patient self-referral
B2.2 What impact will the new policy have on the sources of referral?	**No impact**
B2.3 Is the new policy likely to improve equity of access?	**No impact**
B2.4 Is the new policy likely to improve equality of access and/or outcomes?	**No impact** Please specify:
B3 Implementation	
B3.1 Will commissioning or provider action be required before implementation of the proposition can occur?	**No action required**
B3.2 **Time to implementation:** Is a lead-in time required prior to implementation?	**No - go to B3.4**
B3.3 **Time to implementation:** If lead-in time is required prior to implementation, will an interim plan	Choose an item. If yes, outline the plan:

<table>
<tr><td>for implementation be required?</td><td>Click here to enter text.</td></tr>
<tr><td>B3.4 Is a change in provider physical infrastructure required?</td><td><u>No</u></td></tr>
<tr><td>B3.5 Is a change in provider staffing required?</td><td><u>No</u></td></tr>
<tr><td>B3.6 Are there new clinical dependency and/or adjacency requirements that would need to be in place?</td><td><u>No</u></td></tr>
<tr><td>B3.7 Are there changes in the support services that need to be in place?</td><td><u>Yes</u>
Please specify:
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 e.g. mouth ulcers or stomatitis.</td></tr>
<tr><td>B3.8 Is there a change in provider and/or inter-provider governance required? (e.g. ODN arrangements / prime contractor)</td><td><u>No</u></td></tr>
<tr><td>B3.9 Is there likely to be either an increase or decrease in the number of commissioned providers? If yes, specify the current and estimated number of providers required in each region</td><td><u>No change</u>
Please complete table:
<table>
<tr><td>Region</td><td>Current no. of providers</td><td>Future
State expected range</td><td>Provisional or confirmed</td></tr>
<tr><td>North</td><td></td><td></td><td>select</td></tr>
<tr><td>Midlands & East</td><td></td><td></td><td>select</td></tr>
</table></td></tr>
</table>

	<table><tr><td>London</td><td></td><td></td><td>select</td></tr><tr><td>South</td><td></td><td></td><td>select</td></tr><tr><td>Total</td><td></td><td></td><td>select</td></tr></table> Please specify: No change as adjunctive therapy.
B3.10 Specify how revised provision will be secured by NHS England as the responsible commissioner.	*Select all that apply:* <table><tr><td>Publication and notification of new policy</td><td>☒</td></tr><tr><td>Market intervention required</td><td>☐</td></tr><tr><td>Competitive selection process to secure increase or decrease provider configuration</td><td>☐</td></tr><tr><td>Price-based selection process to maximise cost effectiveness</td><td>☐</td></tr><tr><td>Any qualified provider</td><td>☐</td></tr><tr><td>National Commercial Agreements e.g. drugs, devices</td><td>☐</td></tr><tr><td>Procurement</td><td>☐</td></tr><tr><td>Other</td><td>☐</td></tr></table>
B4 Place-based Commissioning	
B4.1 Is this service currently subject to, or planned for, place-based commissioning arrangements? (e.g. future CCG lead, devolved	**No**

<table>
<tr><td>commissioning arrangements, STPs)</td><td></td></tr>
<tr><td colspan="2">Section C - Finance Impact</td></tr>
<tr><td colspan="2">C1 Tariff/Pricing</td></tr>
<tr><td>C1.1 How is the service contracted and/or charged?
Only specify for the relevant section of the patient pathway</td><td>Select all that apply:
<table>
<tr><td rowspan="3">Drugs</td><td>Not separately charged – part of local or national tariffs</td><td>☐</td></tr>
<tr><td>Excluded from tariff – pass through</td><td>☐</td></tr>
<tr><td>Excluded from tariff - other</td><td>☒</td></tr>
<tr><td rowspan="4">Devices</td><td>Not separately charged – part of local or national tariffs</td><td>☐</td></tr>
<tr><td>Excluded from tariff (excluding ZCM) – pass through</td><td>☐</td></tr>
<tr><td>Excluded from tariff (excluding ZCM) – other</td><td>☐</td></tr>
<tr><td>Via Zero Cost Model</td><td>☐</td></tr>
<tr><td rowspan="8">Activity</td><td>Paid entirely by National Tariffs</td><td>☐</td></tr>
<tr><td>Paid entirely by Local Tariffs</td><td>☐</td></tr>
<tr><td>Partially paid by National Tariffs</td><td>☐</td></tr>
<tr><td>Partially paid by Local Tariffs</td><td>☐</td></tr>
<tr><td>Part/fully paid under a Block arrangement</td><td>☐</td></tr>
<tr><td>Part/fully paid under Pass-Through arrangements</td><td>☐</td></tr>
<tr><td>Part/fully paid under Other arrangements</td><td>☒</td></tr>
</table></td></tr>
<tr><td>C1.2 Drug Costs
Where not included in national or local tariffs, list each drug or</td><td>Estimated annual drug cost per person:
Average dose per day per person = 8.6mg. Average annual cost for a course</td></tr>
</table>

<table>
<tr>
<td>combination, dosage, quantity, list price including VAT if applicable and any other key information e.g. Chemotherapy Regime.
NB discounted prices or local prices must not be included as these are subject to commercial confidentiality and must not be disclosed.</td>
<td>of everolimus per year £48,545
Average annual cost of adjuvant AED therapy per year £658
Total cost £49,203.
Cost of everolimus plus VAT per pack (30 days treatment);
30 x 2mg = £960
30 x 3mg = £1,440
30 x 5mg = £2,250
Per company submission Table 14.
Cost of current treatments - AEDs:
Average cost of AEDs per year per person £1,566.
These are based on the company submission updated for latest BNF prices. Please see resource impact template (‘Assumptions Input’ worksheet – Unit Costs starting at row 72) for further details.</td>
</tr>
<tr>
<td>C1.3 Device Costs
Where not included in national or local tariff, list each element of the excluded device, quantity, list or expected price including VAT if applicable and any other key information.
NB: Discounted prices or local prices must not be included as these are subject to commercial confidentiality and must not be disclosed.</td>
<td>N/A</td>
</tr>
<tr>
<td>C1.4 Activity Costs covered by National Tariffs
List all the HRG codes, HRG descriptions, national tariffs (excluding MFF), volume and other key costs (e.g. specialist top up %)</td>
<td>It is anticipated that treatment would be initiated in an outpatient setting with a further 12 follow up visits per year. For children this would be first attendance at a paediatric neuroscience clinic (day 1, month 1): and 12 subsequent attendances at day 28. For adults attendance is at a neurology clinic on day 1, month 1 with 12 subsequent visits on day 28 of each month. Costs are shown in the table below:
<table>
<tr><td>Description / Treatment function code</td><td>1st attendance (WF01A) (x1) £</td><td>Follow up attendances (WF01A) (x12)</td><td>Total annual cost £</td></tr>
</table>
</td>
</tr>
</table>

		£	
Paediatric epilepsy 223	264	206	2,741
*Adults neurology 400	251	144	1,976
*Treatment function code 400 Neurology (adults) (2016/17 tariff, no 2017/18 equivalent			

It is not anticipated that these costs would be over and above existing monitoring costs for AEDs. Extract from company submission: Although there are drug therapeutic monitoring requirements for everolimus, these are comparable to those already conducted for AED's and therefore we do not anticipate any additional resource use.

Novartis pays for trough monitoring conducted by St Georges University of London. This is open to any trust in UK and is not restricted, therefore the trough monitoring with everolimus has no cost to NHS Trust.

2017/8 Tariffs applicable to potential savings

AA26F Epileptic seizure - best practice tariff	£1,821
TFC 223 Paediatric neurology / 400 Adult neurology – average price – outpatient visit	£216
LA08H Chronic kidney disease interventions with CC score 3-5	£3,885

An average market forces factor (MFF) of 1.0809 is applied to the figures in the above table in the resource impact template (see 'Supporting info – unit costs' worksheet).

C1.5 Will a prior approval mechanism be used to support implementation of the new policy that will require provider compliance to secure reimbursement?	**Yes** Please specify: Blueteq is likely to be used to ensure only patients which fulfil the

<table>
<tr><td></td><td>commissioning criteria as set out in the final policy are prescribed everolimus.</td></tr>
<tr><td colspan="2">C2 Average Cost per Patient</td></tr>
<tr><td>C2.1 What is the estimated cost per patient to NHS England, in years 1-5, including follow-up where required?

Are there any changes expected in year 6-10 which would impact the model?</td><td>
<table>
<tr><td></td><td>Paediatric (£49,203 + 2,741)</td><td></td><td>Adult (£49,203+£1,976)</td></tr>
<tr><td>YR1</td><td>51,944</td><td>YR1</td><td>51,179</td></tr>
<tr><td>YR2</td><td>51,944</td><td>YR2</td><td>51,179</td></tr>
<tr><td>YR3</td><td>51,944</td><td>YR3</td><td>51,179</td></tr>
<tr><td>YR4</td><td>51,944</td><td>YR4</td><td>51,179</td></tr>
<tr><td>YR5</td><td>51,944</td><td>YR5</td><td>51,179</td></tr>
</table>
These figures are from ‘Supporting info – unit costs’ worksheet rows 14 and 15.

The average cost per patient includes follow up in outpatient setting (see C1.4 above). It is not anticipated that follow up and monitoring costs will change significantly over time, or have a significant cost impact over and above the monitoring and follow up needed with current AED’s used in standard care (policy working group meeting 07.09.17). In addition, everolimus is given as an adjunctive treatment to AEDs, therefore the frequency of follow up and monitoring is unlikely to be very different from current practice. Therefore the costs reflected in the resource impact model focus on the treatment cost of everolimus.

Everolimus is likely to become a generic drug within this period (potentially earlier).</td></tr>
<tr><td colspan="2"></td></tr>
</table>

C3 Overall Cost Impact of this Policy to NHS England

C3.1 Specify the budget impact of the proposal on NHS England in relation to the relevant pathway.

Cost pressure

Please specify:

The table below shows the annual cost of treatment over 10 years. These exclude monitoring and adverse events which are not identified as having significantly different costs to current treatment options. Potential savings from hospital admissions and outpatient visits are shown separately. These are based on the primary and secondary outcomes of extension phases in the trials and adjusted for expert opinion to give more cautious estimates.

Estimated budget impact – list prices including VAT

	Resource impact before savings and VAT £000	Admissions and outpatient visits avoided £000	Renal procedures avoided £000	Net resource impact £000	Net resource impact including VAT £000s
Year 1	41,266	1,711		39,556	47,808
Year 2	50,674	2,317		48,357	58,492
Year 5	49,545	2,265	338	46,942	56,851
Year 10	51,951	2,375	41	49,535	59,925

More details on the savings calculations can be found in the 'resource impact template' worksheet of the RIA template between rows 28 and 50. A summary of savings assumptions used is:

- 1 hospital admission avoided per person per year (from average of 4

	admissions for refractory TSC per year without treatment) • 2 outpatient attendances avoided per person per year (from average of 6 attendances for refractory TSC per year without treatment). • Around 36% of adults and 8% of children who have TSC have procedures for angiomyolipomas (AMLs) with around 1/3 requiring surgical intervention (30% used in savings calculations). **The resource impact calculations take into account people stopping treatment and continuing with other AEDs. The figures also reflect that current treatments will still be used in addition to everolimus which is an add-on treatment**. Source: Exist-3 adjusted for expert opinion from PWG. Renal procedures prevented were also potential savings identified at the policy working group and is supported by TOSCA data and data from the EXIST 2 trial. The resource impact model provides further detail on assumptions made and references for potential savings.
C3.2 If the budget impact on NHS England cannot be identified set out the reasons why this cannot be measured.	N/A.
C3.3 If the activity is subject to a change of commissioning responsibility, from CCG to NHS England, has a methodology for the transfer of funds been identified, and calculated?	N/A, no change of commissioning responsibility.
C4 Overall cost impact of this policy to the NHS as a whole	
C4.1 Specify the budget impact of the proposal on other parts of the NHS.	Budget impact for CCGs: **Cost saving**

	Budget impact for providers: **Cost pressure** There could be cost savings to CCGs from a reduction seizures. This is likely to mean fewer hospital admissions, A&E and outpatient visits. There could be a cost pressure to provider services and GPs due to any additional tests, monitoring and follow up needed. These are comparable to those already conducted for AEDs and may not result in additional resource use.
C4.2 Taking into account responses to C3.1 and C4.1, specify the budget impact to the NHS as a whole.	**Cost pressure** Please specify: The figures in C3.1 show that there is resource impact to the commissioner (NHSE) from implementing the policy. The cost of everolimus is at list price, therefore the actual resource impact is likely to be lower. Everolimus is anticipated to come off patent within the10 year timeframe which is likely to further reduce the costs for this treatment.
C4.3 Where the budget impact is unknown set out the reasons why this cannot be measured	Click here to enter text.
C4.4 Are there likely to be any costs or savings for non-NHS commissioners and/or public sector funders?	**Yes** Please specify: There may be wider savings from improved life chances for adults and children who may be able to rely less on services such as social care and specialist education and in some cases may be able to obtain employment.
C5 Funding	

C5.1 Where a cost pressure is indicated, state known source of funds for investment, where identified, e.g. decommissioning less clinically or cost-effective services.	CPAG prioritisation reserve.
C6 Financial Risks Associated with Implementing this Policy	
C6.1 What are the material financial risks to implementing this policy?	Epidemiology of TSC is uncertain. There is also significant uncertainty around the number of people who may receive treatment given the wide range in the number of people who may be clinically eligible. Treatment could be lifelong in some patients. There is uncertainty on the price of everolimus. The most relevant clinical effectiveness evidence is unpublished. There is limited long term evidence (2 years or more) for everolimus use in people with TSC related refractory focal onset seizures. Therefore, consideration should be given to regular monitoring of patients receiving everolimus beyond 2 years for TSC-related refractory focal onset seizures in order to promptly identify any adverse effects of treatment with everolimus.
C6.2 How can these risks be mitigated?	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. A fixed price in addition to a discount could be agreed making everolimus free after a certain period of treatment. The policy could be approved after publication of relevant clinical effectiveness evidence.
C6.3 What scenarios (differential assumptions) have been explicitly tested to generate best case, worst case and most likely total cost scenarios?	The scenario for profile of uptake was discussed with clinical experts at the policy working group meeting. It was highlighted that initial uptake could be as high as 40% of the eligible population due to people awaiting treatment. This is expected to rise to 75% uptake by year 3 as modelled in the resource impact.

C6.4 What scenario has been approved and why?	The scenario of uptake in the resource impact template was agreed with clinical experts at the policy working group on the 7th September 2017. We have used this scenario because it is based on clinical experience and knowledge of each patient group.
C7 Value for Money	
C7.1 What published evidence is available that the treatment is cost effective as evidenced in the evidence review?	Please specify: The clinical evidence review for this technology found no studies relating to cost effectiveness.
C7.2 Has other data been identified through the service specification development relevant to the assessment of value for money?	*Select all that apply:*

Available pricing data suggests the treatment is equivalent cost compared to current/comparator treatment	☐
Available pricing data suggests the treatment is lower cost compared to current/comparator treatment	☐
Available clinical practice data suggests the new treatment has the potential to improve value for money	☐
Other data has been identified	☒
No data has been identified	☐
The data supports a high level of certainty about the impact on value	☐
The data does not support a high level of certainty about the impact on value	☐

	Shepherd et al. (2016) carried out a comparative study on healthcare resource utilisation for people with TSC associated epilepsy in the UK compared with people who did not have TSC associated epilepsy. Total direct costs for people who have epilepsy were 2 times higher for GP visits, 3 times higher for inpatient treatment, four times higher for outpatient treatment and five times higher for primary care drug costs.
C8 Cost Profile	
C8.1 Are there non-recurrent capital or revenue costs associated with this policy?	**No**
C8.2 If yes, confirm the source of funds to meet these costs.	Not applicable

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