SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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everolimus 2mg, 3mg and 5mg dispersible tablets (Votubia®) SMC No 1331/18

Novartis Pharmaceuticals UK Limited

04 May 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the ultra-orphan medicine process

everolimus (Votubia®) dispersible tablets are accepted for use within NHS Scotland.

Indication under review: Adjunctive treatment of patients aged two years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC).

A phase III study identified that everolimus significantly reduced seizure frequency when compared with placebo as adjunctive treatment in patients whose refractory partial-onset seizures, with or without secondary generalisation, are associated with TSC.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of everolimus. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Everolimus (Votubia®) dispersible tablets are also licensed for use in treatment of subependymal giant cell astrocytoma (SEGA) associated with TSC. The manufacturer's submission related only to the use of this product in refractory partial-onset seizures associated with TSC.

Chairman,
Scottish Medicines Consortium

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Indication

Adjunctive treatment of patients aged two years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC).[1]

Dosing Information

The recommended starting dose of everolimus for the treatment of patients with seizures is shown in Table 1 below. Different strengths of everolimus dispersible tablets can be combined to attain the desired dose.[1]

Table 1: Everolimus starting dose.

Age	Starting dose without co-administration of CYP3A4 / PgP inducer	Starting dose with co-administration of CYP3A4 / PgP inducer
<6 years	6mg/m^2	9mg/m^2
≥6 years	5mg/m^2	8mg/m^2

Abbreviations: CYP: Cytochrome p450 3a4; PgP: P-glycoprotein

Everolimus whole blood trough concentrations should be assessed at least one week after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 15ng/mL. The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability. Individualised dosing should be titrated by increasing the dose by increments of 1 to 4mg to attain the target trough concentration for optimal clinical response. Efficacy, safety, concomitant therapy, and the current trough concentration should be considered when planning for dose titration. Individualised dose titration can be based on simple proportion:

$$new\ everolimus\ dose = current\ dose \times \left(\frac{target\ concentration}{current\ concentration}\right)$$

Treatment with everolimus should be initiated by a physician experienced in the treatment of patients with tuberous sclerosis complex (TSC) and therapeutic drug monitoring. Further details are provided in the summary of product characteristics (SPC).[1]

Product availability date

December 2016

Everolimus meets SMC ultra-orphan criteria for this indication.

Background

Everolimus is a selective mammalian target of rapamycin (mTOR) inhibitor which has been shown to have anti-seizure activity. It is the only medicine licensed in the UK for treatment of refractory partial-onset seizures associated with tuberous sclerosis complex (TSC). Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. This interferes with the translation and synthesis of proteins involved in the cell cycle, angiogenesis and glycolysis.[1]

It is common for patients with TSC to develop epilepsy and neuropsychiatric conditions. A variety of seizure types have been reported, complex partial-onset seizures and infantile spams have previously been reported as the most common.[2] Seizures associated with TSC are treated with anti-epileptic medicines or non-pharmacological methods such as epilepsy surgery, vagal nerve stimulator or ketogenic diet. [2, 3]

Everolimus for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

TSC is a rare and debilitating genetic disease caused by a deficiency in either the tuberous sclerosis 1 gene (TSC1), the tuberous sclerosis 2 gene (TSC2), or both. Deficiency of either gene leads to upregulation of mTOR-raptor signal transduction complex 1 (mTORC1) resulting in abnormal cellular growth, proliferation, and protein synthesis, which can cause a variety of benign tumours (hamartomas) in multiple organ systems, including lesions in the brain. Hamartomas in the brain usually present as subependymal nodules. Growth of the subependymal nodules leads to them becoming subependymal giant cell astrocytoma (SEGA) in up to 20% of patients with TSC, which is a considerable risk to the patient and could potentially result in sudden death secondary to acute hydrocephalus. The majority of patients with TSC also have numerous bilateral renal angiomyolipoma.[2]

Seizures associated with TSC are a potentially life threatening condition with the main causes of death being status epilepticus and therefore the objective of treatment is seizure control.[2] It has been estimated that over 60% of patients have disease resistant to standard therapy.[3] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely treatment of refractory partial-onset seizures, with or without secondary generalisation, associated with TSC.

A patient and clinician engagement (PACE) meeting was held to consider the added value of everolimus in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the high frequency of seizures experienced by patients with TSC. TSC-related epilepsy can have a severely negative impact on physical and mental health. Many patients with TSC have neurodevelopmental problems and learning disabilities and uncontrolled epilepsy is thought to be a major contributing and exacerbating factor. Suffering from frequent seizures means that patients can often have very poor sleep, extreme tiredness and suffer from anxiety or distress. They are also at increased risk of falls and injury. Patients are likely to need a carer with them at all times. TSC-related seizures impact on their independence, the ability to work or attend school and participate in family and social activities.

Impact of new technology

Summary of evidence on comparative efficacy

EXIST-3 was a phase III, randomised, double-blind, placebo-controlled study in 366 patients aged two to 65 years of age with TSC and treatment-resistant partial onset seizures (≥16 in an eight-week baseline phase). The study was conducted between April 2013 and October 2015 (data cut-off).[2, 3]

At the end of the eight-week baseline phase, eligible patients were randomised into the core phase in a 1:1:1 ratio to receive everolimus titrated to a target trough concentration (C_{min}) of 3 to 7ng/mL (low-exposure everolimus), everolimus titrated to a target C_{min} of 9 to 15ng/mL (high-exposure everolimus) or placebo, in addition to a stable regimen of one to three anti-epileptic medicines. No more than one of these could be a strong CYP3A4 inducer (such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone). Randomisation was stratified by age subgroup (<6 years, 6 to <12 years, 12 to <18 years, and ≥18 years). Dose adjustments to attain the target C_{min} were made during the first six weeks of the core phase (up to three adjustments could be made), and as needed during the subsequent 12-week maintenance period. Dosage interruptions or adjustments were allowed for patients who did not tolerate the protocol-specific dosing schedule.[2, 3] Rescue medication was permitted for a maximum of six days during the baseline phase of the study and no more than seven consecutive days or a total of 14 cumulative days during the core phase. Use of rescue medications for a longer duration was considered as treatment failure and the patient was to be discontinued from study therapy. Local practice guided the choice of rescue medications (for example buccal midazolam, rectal diazepam and other benzodiazepines).[2]

The primary outcome was the change from baseline in seizure frequency for each of the two everolimus arms compared with placebo during the 12-week maintenance period of the core phase. A seizure diary was completed by patients or their carers recording the type and frequency of seizures. These were entered into a seizure identification form and separated into probable seizures (>80% likelihood) and questionable seizures (50% to 80% likelihood) by the investigators. Seizure classification and likelihood of probable or questionable seizure was confirmed by independent reviewers (epileptologists from the Epilepsy Study Consortium).[2, 3]

Median seizure frequency (per 28 days) during the baseline phase of the study was 34 in the low-exposure everolimus group, 38 in the high-exposure everolimus group and 42 in the placebo group. [2, 3]

The proportion of patients achieving the primary outcome of at least a 50% reduction in seizure frequency during the 12-week maintenance period was 28% (33/117) in the low-exposure everolimus group, 40% (52/130) in the high-exposure everolimus group and 15% (18/119) in the placebo group ($p=0.0077$ and $p<0.0001$ for the low-exposure and high exposure everolimus groups when compared with placebo).[2, 3] The median percentage reduction in seizure frequency from baseline during the 12-week maintenance period was 29%, 40% and 15% in the low-exposure everolimus, high-exposure everolimus and placebo groups respectively ($p=0.0028$ and $p<0.0001$ for the low-exposure and high-exposure everolimus groups when compared with placebo). [2, 3]

Rescue medication was used in a greater proportion of patients in the high-exposure everolimus group (18%) compared with low-exposure everolimus (10%) and placebo (12%) groups. The majority of rescue medication consisted of one dose of a benzodiazepine.[2] Selected secondary outcomes are detailed below in Table 2.

Table 2: EXIST-3 selected secondary outcomes during the 12-week maintenance period.[2, 3]

	Low-exposure everolimus	High-exposure everolimus	Placebo
Proportion of patients achieving at least 25% reduction in seizures	52% (61/117)	70% (91/130)	38% (45/119)
Seizure-free rate (patients remaining seizure free during the maintenance period)	5.1% (6/117)	3.8% (5/130)	0.8% (1/119)
Median number of seizure free days per 28 days (change from baseline)	2	4	0.5

Quality of life data were collected using QOLCE (patients aged <11 years), QOLIE-AD-48 (patients aged ≥11 to <18 years) and Qolie-31-P (patients aged ≥18 years) questionnaires; these did not identify any significant differences between groups.

After completion of the core phase of EXIST-3, all patients were offered the option to continue in the ≥48-week extension phase. Nearly 90% (342/366) entered the extension phase.[3] Patients received everolimus, titrated by automated Interactive Response Technology (IRT), to achieve a C_{min} of 6 to 10ng/mL and this was followed by non-automated titration by the investigator to achieve C_{min} of 3 to 15ng/mL. Data were available for 298 and 163 patients at 1 and 2 years, respectively. The response rate (percentage of patients achieving ≥50% reduction in seizures) was 47% after one year and 58% after two years. The median percentage reduction in seizure frequency was 47% after one year and 57% after two years.[4]

Summary of evidence on comparative safety

Adverse events were reported in 92% (108/117) of patients in the low-exposure everolimus group, 95% (123/130) in the high-exposure everolimus group and 77% (92/119) in the placebo group. Grade 3 or 4 adverse events were reported in 18% (21/117), 24% (31/130) and 11% (13/119) of the low-exposure everolimus, high-exposure everolimus and placebo groups respectively. Serious adverse events were reported in 14% (16/117 and 18/130) of patients in the low-exposure and high-exposure everolimus groups and 3% (3/119) of patients in the placebo group. Adverse events leading to discontinuation occurred in 5% (6/117), 3% (4/130) and 2% (2/119) of patients in the low-dose everolimus, high-dose everolimus and placebo groups respectively. The most common reason for this was stomatitis occurring in two patients in each of the everolimus groups.[3]

Stomatitis was the most frequently reported adverse event in the everolimus groups occurring in 55% (64/117) of the low-exposure group and 64% (83/130) of the high-exposure group compared with 9% (11/119) of patients in the placebo group. Other commonly reported adverse events were diarrhoea (17%, 22% and 5%), nasopharyngitis (14%, 16% and 16%), upper respiratory tract infection (13%, 15% and 13%) and pyrexia (20%, 14% and 5%).[3]

The most commonly reported adverse events reported in the 361 patients who received treatment in the long-term extension study were stomatitis (35%), pyrexia (35%), diarrhoea (28%), mouth ulceration (28%), nasopharyngitis (24%) and upper respiratory tract infection (22%).[4] Two deaths occurred during the extension study that were thought to be due to the study medication. They were both children, the first death was due to pneumonia and the second was septic shock.[4]

Everolimus has immunosuppressive properties and may increase the risk of infections. The SPC recommends dose adjustments if the following adverse events occur: non-infectious pneumonitis, stomatitis, other non-haematological toxicity, metabolic events, thrombocytopenia and neutropenia.[1]

Summary of clinical effectiveness issues

The pivotal study, EXIST-3, identified a statistically significant reduction in seizure frequency in patients in both the low-exposure and high-exposure everolimus groups when compared with placebo, reported as response rate (the proportion of patients achieving at least a 50% reduction in seizure frequency) and median percentage reduction in seizure frequency.

Due to an error with the IRT system, everolimus doses were not titrated for the first five months of the study. The number of patients to be included in the high-exposure everolimus arm was increased to prevent loss of power.

EXIST-3 recruited patients aged two to 65 and the number of patients in each age group was fairly small, the majority of patients (>80%) in all groups were under 18 years old.[2, 3] The European Medicines Agency (EMA) noted that subgroup analyses according to age identified higher response rates and increased seizure reduction for all age categories in both everolimus groups compared with placebo.[2]

Dosing of everolimus should be titrated to attain trough concentrations of 5 to 15ng/mL whereas in EXIST-3 the desired trough concentrations were 3 to 7mg/m^2 and 9 to 15mg/m^2 in the low-exposure and high exposure groups respectively. Patients were excluded if they had an episode of status epilepticus within one year before the study which may mean that some of the relevant patient population have been excluded.

Median baseline seizure frequency was slightly higher in the placebo group, however the effect was small and not considered to be clinically relevant. Efficacy outcomes were from the 12-week maintenance period of the core phase of the study which is a relatively short period of time for a condition that will potentially require lifelong treatment. There are, however, long-term results for up to two years from the extension study. The proportion of patients who were seizure-free during study maintenance phase was low however included patients had refractory seizures and the mean baseline seizure frequency per 28 days was between 34 and 42 across groups. Rescue medication was used more frequently in the high-exposure everolimus group. This was almost always one dose of a benzodiazepine and was not expected to have affected the overall study results.[2]

There is a lack of quality of life data from EXIST-3. There were marginal changes for data collected in all three treatment arms. No meaningful differences between the three treatment arms for patients <18 years old was observed. Numerical differences in favour of placebo were observed in the ≥18 age category during the core phase of the study however only approximately half of patients completed the questionnaire at baseline and the end of the core phase and the EMA noted that there were too many missing values and that a high potential for selection bias regarding questionnaire completion can be assumed. Evaluable data were only available for 10 to 12 patients per group and high variability was observed for respective results.[2]

Neurocognitive, neurobehavioural and neurodevelopmental outcomes were planned to be collected in EXIST-3[5] however no results for these health outcomes were presented. It is noted in the published paper that in relation to completion of the Vineland II Adaptative Behavior Scale *"the substantial intellectual disability in the study population resulted in frequent failure of investigators to perform the survey at baseline and yielded profound flooring (ie, scores below which the test can no longer distinguish levels of behavioural attainment) in many surveys, limiting the interpretation of results."*[3]

Best supportive care, which includes anti-epileptic medication, has been included as the only relevant comparator for this submission. The majority of patients will be treated with anti-epileptic medication however non-pharmacological methods such as epilepsy surgery, vagal nerve stimulator or ketogenic diet are also potential comparators in a small proportion of patients.

Clinical experts consulted by SMC considered that everolimus is a therapeutic advancement and that the place in therapy would be as a treatment option for patients with refractory partial-onset seizures associated with TSC. Everolimus is administered orally which would allow administration at home by patients or carers. It is a dispersible tablet which may be beneficial for patients who have difficulty swallowing tablets. Therapeutic drug monitoring of trough levels is required which may impact on the patient, carers and the service. Everolimus has immunosuppressive properties and may increase the risk of infections, stomatitis and neutropenia.[1, 2] Women of childbearing potential must use a highly effective method of contraception while receiving everolimus, and for up to eight weeks after ending treatment.[1]

At the PACE meeting, it was noted that a reduction is seizures is likely to lower the risk of seizure-associated co-morbidities and mortality. There may be an additional benefit on patients' quality of life by improving sleep, memory and learning. Starting everolimus early in children could potentially have benefits in reducing the development or severity of autism, attention deficit hyperactivity disorder or challenging behavior associated with neurodevelopmental delay. Reducing the frequency of seizures could allow patients to become more independent, for example increasing their ability to self-care, work or attend school and participate in family or social activities. This may improve their mood and mental health. Everolimus may also confer benefits on other manifestations of TSC.

Patient and clinician engagement (PACE)

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of everolimus as an ultra-orphan medicine in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- TSC is a long-term debilitating condition and the majority of patients experience frequent seizures which are likely to have a severely negative impact on their physical and mental health. Many patients have neurodevelopmental problems and learning disabilities and uncontrolled epilepsy is thought to be a major contributing and exacerbating factor.

- There is unmet need in the treatment of TSC-related epilepsy. Anti-epileptic medications are used as first-line treatment however it is estimated that approximately 60% of patients have seizures that are uncontrolled by these medications. Other treatment options are surgery and a ketogenic diet but patients may be unsuitable for these treatments or they may be ineffective.

- Evidence is available demonstrating that everolimus significantly reduces seizures in patients with TSC. It has a novel mechanism of action specific to this condition and would provide another treatment option for this refractory patient group.

- Everolimus may allow patients to manage their condition better. Reducing seizures could increase independence and improve quality of life, reduce anxiety, improve sleep, memory and concentration. This could allow patients to attend school or potentially work and participate in family activities. Families of patients with TSC-associated seizures could benefit from reduced caring responsibilities, allowing them to spend more quality time with other family members, work or study.

- The side effect profile of everolimus appears manageable. It was noted that everolimus requires dose titration according to blood levels and close monitoring for potential adverse effects and this may require frequent hospital visits until therapeutic levels are reached.

- The place in therapy for everolimus would be adjunctive treatment of patients aged two years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with TSC.

Additional Patient and Carer Involvement

We received a patient group submission from the Tuberous Sclerosis Association, which is a registered charity. The Tuberous Sclerosis Association has received 6% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the

Tuberous Sclerosis Association participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Value for money

The submitting company presented a cost-utility analysis of everolimus for the adjunctive treatment of TSC associated refractory partial-onset seizures, with or without secondary generalisation among patients aged 2 years and older. The comparator was best supportive care (BSC), described as symptomatic treatment with anti-epileptic medication.

In the analysis, patients received either an everolimus dose of 7.2mg/m^2 alongside BSC with anti-epileptic medication, or BSC with anti-epileptic medication. Information on the individual anti-epileptic medications includedas BSC was provided by data collected from the EXIST-3 study. The dose used in the model was also pooled from data in this study, as there were two everolimus treatment arms; "low exposure" with a mean dose of 5.8mg/m^2 or "high exposure" with a mean dose of 8.5mg/m^2.

Response was defined as 50% or greater mean reduction in seizure frequency. An initial decision tree was used to provide information on initial response for the first 18 weeks, based on the core phase of the EXIST-3 study. Following this, the model cohort entered a Markov model with 12 week cycle lengths, where states were defined as categories of % mean reduction in seizure frequency and patients could transition between these states every 12 weeks for a period of up to four years. Beyond this time period, it was assumed that their most recent response state was sustained until the end of the time horizon in the model, which was a lifetime (100 years) in the base case but varied in the scenario analysis.

The model assumed loss of response results in returning to 0% mean reduction in seizure frequency and cessation of everolimus treatment among those receiving this treatment. It assumed that response with everolimus treatment results in a reduction in the adjunctive anti-epileptic medications being used by this group of patients, but that BSC group participants would continue receiving all anti-epileptic medications received at baseline, regardless of response status.

Utility data were drawn from the literature, namely a sub study from a chart review conducted using the Health Utilities Index (HUI3) in a Dutch population. The choice was justified by the submitting company given the outcome measures used by the EXIST-3 study to measure health-related quality of life. Other EQ-5D data are also available in the literature for an epilepsy population but without TSC. The chart review included a subgroup of patients who did not have epilepsy, but of the patients who did, mean overal utility was 0.31 (95% CI, 0.25, 0.38) and this was used in the cost-effectiveness model. A small proportion of patients had epilepsy only (ie no renal angiomyolipoma and/or SEGA in addition to epilepsy).

Costs in the model included the cost of the treatment, other medicines costs, epilepsy monitoring and management costs, the costs of adverse events and the costs associated with other TSC manifestations, namely SEGA, renal angiomyolipoma and facial angiofibroma (FA).

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

The results of the base case and key sensitivity and scenario analyses are presented in the Table below.

Table 3: Base case and sensitivity analysis results (with PAS)

Intervention	**ICER (Incremental cost effectiveness ratio)**	
Base case	£26,271	
Probabilistic sensitivity analysis	£15,922	
10 year time horizon	£80,417	
20 year time horizon	£51,384	
Exclude effect on other TSC manifestations	£35,422	
Exclude effect on TSC neuropsychiatric comorbidities	£31,489	
Exclude effect on other TSC manifestations and neuropsychiatric comorbidities	£41,134	
Deterministic (one-way) sensitivity analysis (with PAS)		
Parameter	**'Lower' value ICER**	**'Upper' value ICER**
Distribution of patients in epilepsy control categories – everolimus plus BSC	£73,475	£22.768
% whose seizure type was secondary generalised: convulsive at 66 weeks - BSC (mean)	£49,194	£9,458
Prevalence of SEGA in the 14-18 years of age group	£30,784	Dominant
Adverse event discontinuation - everolimus plus BSC	£44,558	£15,983
% whose seizure type was secondary generalised: convulsive at 66 weeks – everolimus plus BSC (mean)	£13,327	£41,224
Distribution of patients in epilepsy control categories – BSC	£14,292	£31,681
Mean seizure frequency reduction of 0% - BSC	£28,066	£43,994

The QALY gains identified in the base case are solely due to improvement in quality of life as no life year gains were found. Sensitivity of the results to changes in the time horizon as shown by the scenario analysis is indicative of the time required to accrue the QALY gains. Expert advice provided to SMC indicates life expectancy can be normal in the absence of astrocytomas. Mortality estimates in the model accounted for this and other TSC-associated mortality.

The probabilistic sensitivity analysis found that the probability of everolimus plus BSC being more cost-effective than BSC alone was 67% at a willingness-to-pay threshold of £30,000 per QALY gained and this was 77% at the £50,000 threshold.

The deterministic sensitivity analysis results are in line with expectations in terms of the direction of effect, but the magnitude of effect shows the sensitivity of the economic case to the relative effectiveness of everolimus on epilepsy control, epilepsy management costs for more severe seizure types, the prevalence of the SEGA comorbidity and the costs associated with continued everolimus in the absence of adverse event discontinuation.

Additional sensitivity analysis around dosing was considered important given the pooling of results from two arms of the EXIST-3 study. This was provided by the submitting company on request and found to be reasonable.

Treatment monitoring frequencies in the model were undertaken for anti-epileptic medicines every 12 weeks (with more frequent monitoring every 6 weeks for a subgroup of listed anti-epileptic medicines). According to expert advice provided to SMC, treatment response would be likely to be clinically reviewed approximately once every six months in secondary care. On this basis, the modelling assumption is likely to be conservative. However, it is clinically understood that where everolimus has been used in other disease areas, additional monitoring has been required owing to its mechanism of

action. This does not appear to have been accounted for in the economic evaluation and the overall effect is unclear.

Key limitations of the model are

- The utility data were sourced from a sub-study of a chart review of Dutch patients with TSC. Given the use of these data, compared with more widely available EQ-5D data for a general epilepsy population refractory to anti-epileptic medicines, additional sensitivity analysis should have been reported.
- Assumptions about the probabilities of having other TSC manifestations and/or TSC-associated neuropsychiatric comorbidities, and the unit costs associated with the presence of these, have a considerable impact on the results. Key scenario analysis showed that removing costs and effects associated with these groups had a relatively large impact on the ICER.
- Assumption about how anti-epileptic medicines are used in the BSC group compared with everolimus is potentially important. Expert advice has indicated that patients in Scotland would be expected to remain on anticonvulsants whether they receive everolimus or not. This impacts on the other medicine costs for the BSC group in the model and has implications for the relative effectiveness of everolimus shown in the model. However, sensitivity analysis was subsequently provided which showed this assumption was not a key driver of the model.

Impact beyond direct health benefits and on specialist services

Family and carers of patients with TSC often experience anxiety and fatigue relating to the patients' health and safety and reducing the frequency of seizures may alleviate this to some extent. Improved seizure control should also reduce the frequency and burden of seizure-related hospital visits. Children of patients with TSC may provide care for their parents and reducing seizures may reduce the burden on them.

Everolimus requires dose titration according to blood levels and close monitoring for adverse effects which would impact on the patient and their family / carers and have service implications. This may have a particular impact on children where monitoring of blood levels can be problematic. A PACE clinician noted that monitoring of everolimus levels is not currently widely available which could potentially lead to delays in obtaining results.

Costs to NHS and Personal Social Services

The submitting company estimated there would be 60 patients eligible for treatment with everolimus rising to 68 patients in year 5. The estimated uptake rate was 25% in year 1 (13 patients) and 45% in year 5 (25 patients).

The submitting company did not estimate any costs outside the NHS.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

Conclusion

The Committee also considered the benefits of everolimus in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for absence of other treatments of proven benefit was satisfied. In addition, as everolimus is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted everolimus for use in NHS Scotland.

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN) published guidelines for the diagnosis and management of epilepsy in adults (SIGN 143) in 2015 but these do not specifically mention patients with refractory POS associated with TSC.[6] The SIGN guideline on epilepsy in children has been withdrawn and an update is currently underway, but is unlikely to deliver until 2019.

The international clinical guidelines developed at the TSC Consensus Meeting for SEGA and Epilepsy Management (2012) provide the following general treatment recommendations for patients with focal seizures:

- First line: vigabatrin for focal seizures before the age of 1 year. Other anti-epileptic medicines that enhance gamma-aminobutyric acid (GABA)ergic inhibition (e.g. topiramate and carbamazepine) after the age of 1 year
- Second line: surgery – usually restricted to those with focal stereotypical seizures and a single EEG focus and is contraindicated in the case of multiple seizure types
- Third line: ketogenic diet, VNS, other anti-epileptic medicines used in focal seizures.[7]

Additional information: comparators

Everolimus is the only medicine licenced in the UK for treatment of refractory partial-onset seizures associated with TSC.

Cost of relevant comparators

<table>
<tr><th>Medicine</th><th>Dose Regimen</th><th>Cost per year (£)</th></tr>
<tr><td>Everolimus (Votubia® dispersible tablets)</td><td>
<table>
<tr><td>Age</td><td>Starting dose without co-administration of CYP3A4/PgP inducer</td><td>Starting dose with co-administration of CYP3A4/PgP inducer</td></tr>
<tr><td><6 years</td><td>6mg/m^2</td><td>9mg/m^2</td></tr>
<tr><td>≥6 years</td><td>5mg/m^2</td><td>8mg/m^2</td></tr>
</table>
By mouth, once daily, titrated to response within the target trough plasma concentration range of 5 to 15ng/mL.
</td><td>£23,296 to £77,896</td></tr>
</table>

Costs calculated using the median dose received by patients in the high-exposure everolimus group in the EXIST-3 study (7.5mg/m^2/day). Costs from eVadis on 02 February 2018. Costs do not take any patient access schemes into consideration.

References

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This assessment is based on data submitted by the applicant company up to and including 16 March 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates

separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.