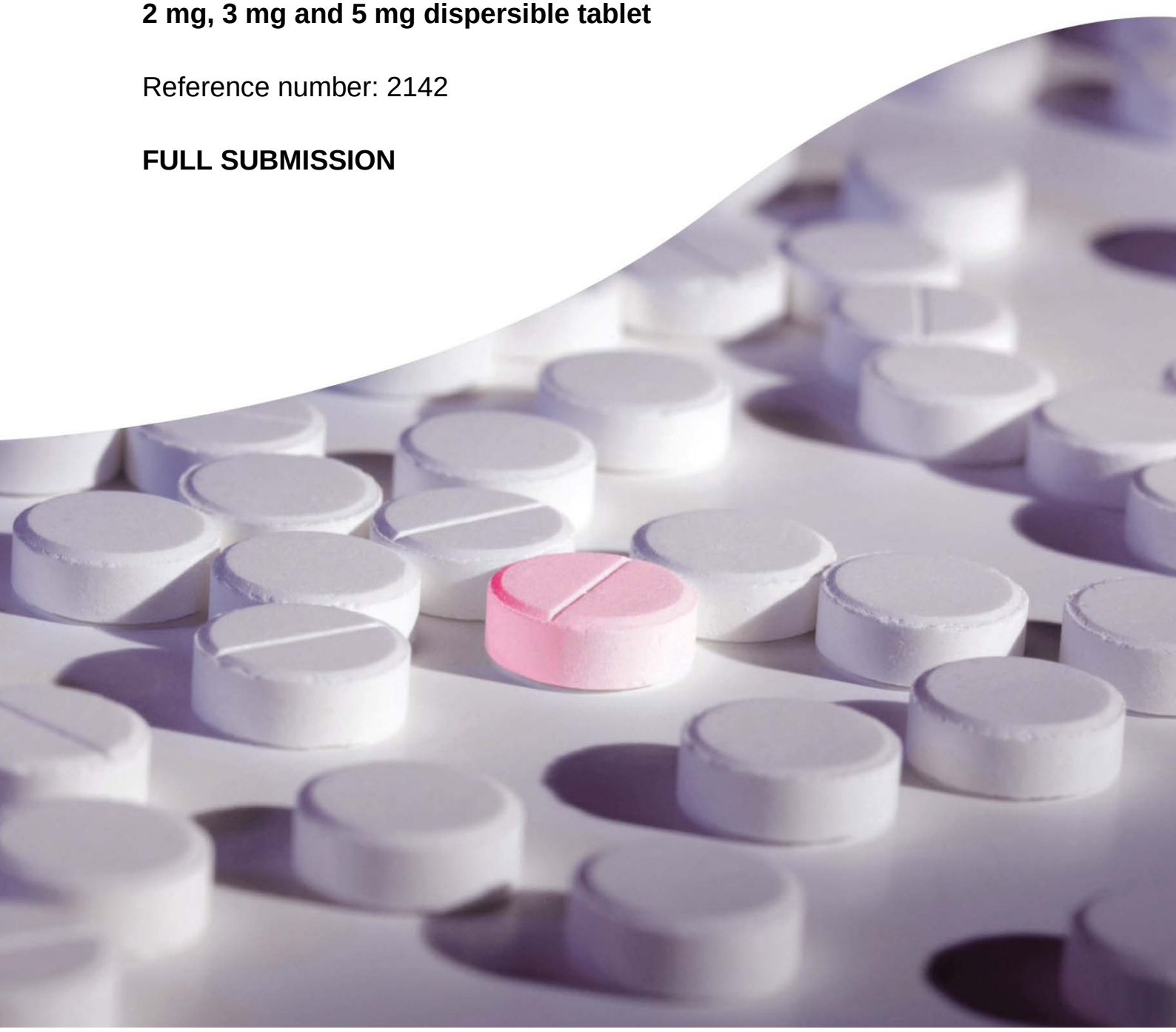
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Everolimus (Votubia®)
2 mg, 3 mg and 5 mg dispersible tablet

Reference number: 2142

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Everolimus (Votubia®) 2 mg, 3 mg and 5 mg dispersible tablet

1.0 KEY FACTS

Assessment details	Everolimus (Votubia®) for adjunctive treatment of patients aged 2 years and older whose refractory partial onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC).
Current clinical practice	There are currently no other licensed medicines available for the treatment of refractory seizures associated with TSC. Current clinical practice is limited to best supportive care which consists of anti-epileptic drugs (AEDs), either alone or in combination with other AEDs. Welsh clinical experts indicate a significant unmet need in this population and an absence of any adjunctive treatments for patients who remain with severe disabling drug resistant seizures with currently available AEDs.
Clinical effectiveness	The main evidence comes from a phase III double-blind study, and its respective open label extension phase, comparing high exposure everolimus, low exposure everolimus and placebo. At the end of the 12-week maintenance period patients showed significantly reduced seizure frequency (measured as percentage experiencing ≥ 50% reduction in seizure frequency and median percentage reduction in seizure frequency) in the everolimus treatment arms compared to placebo. Response rates (percentage of patients experiencing ≥ 50% reduction in seizure frequency) and median percentage reductions in seizure frequency with everolimus further improved during the extension phase (minimum 48 weeks). Treatment with up to three AEDs was allowed in all study groups (everolimus and placebo), in line with the intended positioning of everolimus as an adjunctive treatment.
Cost-effectiveness	The company submission reports the results of a cost-utility analysis comparing dispersible Votubia® tablets in combination with best supportive care (BSC) with BSC as a treatment for patients with refractory partial-onset seizures (POS) associated with tuberous sclerosis complex (TSC). The company base case suggests an incremental cost-effectiveness ratio (ICER) of [commercial in confidence figure removed] /quality-adjusted life-year (QALY) gained, when a PAS discount is applied. The company submission does not include an executable model thereby preventing: a comprehensive critique and validation of the model and the results produced; AWTTC

	exploration of uncertainty, and the impact on the ICER of alternative AWTTC-preferred assumptions and scenarios. The cost-effectiveness estimates reported are therefore subject to considerable uncertainty and are restricted to company conducted analyses that cannot be verified.
Budget impact	The company estimates that eight patients are eligible to receive treatment with Votubia® in Wales in Year 1, increasing to 15 patients in Year 5. The company base case suggests an additional cost based on the PAS of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The number of patients expected to receive Votubia® and the dosing used in the analysis are subject to uncertainty. AWTTC consider a higher budget impact than that estimated is plausible.
Additional factors to consider	The company consider Votubia® eligible to be considered as an ultra-orphan medicine. AWTTC considers Votubia® eligible to be appraised as an orphan medicine. However, it is uncertain whether it meets the population criteria for an ultra-orphan medicine when all licenced indications are taken into account.

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd[1] and an evidence search conducted by AWTTC on 27 April 2021.

2.0 BACKGROUND

2.1 Condition and clinical practice

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder associated with mutations affecting TSC1 and TSC2[2]. Deficiency of either gene leads to over-activation of the mammalian target of rapamycin (mTOR) pathway (specifically mTOR complex-1), resulting in abnormal cellular growth and proliferation, and protein synthesis, which can cause the development of non-cancerous growths in multiple organ systems throughout the body (kidney, brain, skin, eye, lung and heart)[2].

Epilepsy is a common manifestation of TSC occurring in up to 84% of TSC patients in the UK[3]. Diagnosis of TSC-associated epilepsy normally occurs within the first few years of life (66% in first year of life and 80% by age 3)[4]. Most patients with early-onset epilepsy present with infantile spasms or focal (or partial) seizures[3,4]. Infantile spasms and refractory seizures are related to intellectual disability[5] and sudden unexpected death in epilepsy (SUDEP) in infants and children with TSC[6].

Treatment of TSC-associated epilepsy aims to stop seizures as early as possible after diagnosis. Early management of seizures is important in preventing and reducing the cognitive and neurological and psychiatric consequences from refractory seizures[7]. Long term intellectual development is thought to be improved if seizure treatment starts as soon as a child is diagnosed with epilepsy and when it provides a prompt response[8]. There is no TSC specific anti-epilepsy medication so anti-epileptic drugs (AEDs), either alone or in combination with other AEDs, are the most common treatment in UK clinical practice[9]. No consensus regarding the most effective AED has

been reached, with the exception of vigabatrin as first line treatment for infantile spasms. Other treatment options include epilepsy surgery, vagal nerve stimulation or ketogenic diet[10,11].

However, over one third of patients have been reported to develop refractory epilepsy, with their seizures not successfully controlled by AEDs[4]. Seizures are considered to be refractory when two different AEDs given at therapeutic doses have failed to control a person's seizures (also known as uncontrolled or intractable)[9]. The proportion of TSC patients with uncontrolled seizures who subsequently achieve seizure remission following further intervention (including surgery) has been reported to be as low as 19%[4].

Current treatment in Wales consists of available AEDs, so everolimus would be an adjunctive treatment for resistant epilepsy in TSC. Welsh clinical experts estimate that approximately 90% of individuals with TSC have epilepsy, 30% of whom would develop refractory epilepsy with the currently available treatment options, suggesting that there is a substantial unmet need for new treatment options.

2.2 Medicine

Everolimus is a selective inhibitor of the serine-threonine kinase mTOR within the mTOR complex-1 (mTORC1)[2]. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTORC1 activity and blocks the over-activation which is thought to be the cause of seizures in people with TSC; and can be considered as a disease modifying agent for TSC.

Everolimus dispersible tablets (Votubia®) was granted marketing authorisation by the European Medicines Agency (EMA) in January 2017 for the adjunctive treatment of patients aged 2 years and older with refractory seizures associated with TSC. Everolimus is the first licensed medicine for this indication under consideration.

The recommended starting dose for everolimus for the treatment of patients with TSC and refractory seizures ranges from 5 mg/m^2 to 9 mg/m^2 and is calculated based on body surface area, age, and whether or not the dose is to be co-administered with a CYP3A4/PgP inducer[12]. Everolimus is not curative, and treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs[12].

2.3 Comparators

The company submission includes best supportive care as the comparator, which includes other anti-epileptic medication (AEDs).

2.4 Guidance and related advice

- UK TSC guidelines (2019)[13]
- NHS England (2018) commissioning guidelines[9]
- Scottish Medicines Consortium Advice No. 1331/18 (2018) [14]
- Scottish Intercollegiate Guidelines Network (SIGN) guidance 159 (2021)[15]
- NICE clinical guideline 137 – Epilepsies: diagnosis and management[8]

European recommendations

- European Consensus Meeting, Management of Epilepsy Associated with Tuberous Sclerosis Complex (2018)[16]
- International TSC consensus Conference (2012)[17]

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, everolimus (Votubia®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company confirms that everolimus (Votubia®) may be supplied by a home healthcare provider and that an arrangement is already in place for Wales.

3.0 CLINICAL EFFECTIVENESS

The company's submission includes evidence from a phase III, double-blind, randomised controlled study (EXIST-3) and its respective open label extension study, both summarised below.

3.1 EXIST-3

This was a prospective, randomized, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of two trough ranges of everolimus given as adjunctive therapy in patients aged 2 to 65 years with a confirmed diagnosis of TSC and treatment resistant epilepsy[18].

Patients reported 16 or more seizures during the eight-week baseline phase (with no continuous 21-day seizure-free period) and were receiving between one and three AEDs at a stable dose for at least 12 weeks before randomisation. All patients were permitted to continue this AED treatment alongside the study drug (everolimus or placebo)[18].

At the end of the eight-week baseline phase, eligible patients (n=366) were randomised 1:1:1 into the core phase to receive placebo, everolimus titrated to a target trough concentration (C_{min}) of 3-7 ng/mL (low exposure everolimus), or everolimus titrated to a target C_{min} of 9-15 ng/mL (high exposure everolimus)[18]. Randomisation was stratified by age subgroup (<6 years, 6 to <12 years, 12 to <18 years, and ≥18 years). After completing the 18-week double-blind period (six weeks titration followed by a 12 week maintenance phase), patients could enter an additional minimum 48-week, open-label extension period in which all patients received everolimus treatment[19].

Study medication consisted of everolimus 2 mg dispersible tablet and identical placebo dispersible tablets[18]. For the first six weeks of the study, the dose of everolimus was slowly increased to attain the target C_{min} (a maximum of three dose adjustments). That therapeutic dose was then maintained for the following 12 weeks. Rescue medication to provide additional seizure control 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[18].

The primary endpoint was the reduction of TSC seizure frequency[18]. This was measured as both percentage of patients demonstrating ≥ 50% reduction in seizure frequency at the end of the 12-week maintenance phase compared to baseline (response rate) and as a median percentage reduction in seizure frequency. Patients or their caregivers completed a seizure diary, in which they recorded seizure types and frequencies. These were entered into a seizure identification form and separated into probable seizures (>80% likelihood of being an epileptic seizure) and questionable seizures (50–80% likelihood) and confirmed by independent reviewers. Only probable seizures were counted towards the primary outcome[18].

Median seizure frequency (per 28 days) during the baseline phase of the study was 34.5 in the low exposure everolimus group, 37.8 in the high-exposure everolimus group and 42.0 in the placebo group[18].

Primary outcomes are detailed in Table 2, and show a significantly greater response rate (reduction in seizure frequency ≥ 50% from baseline) in the everolimus treatment arms (low exposure: 28.2%; high exposure: 40.0%) compared to placebo (15.1%) at the end of the 12-week maintenance period. Everolimus was also associated with a significantly greater median percentage reduction in seizure frequency. All sensitivity analyses as well as per protocol analysis produced results which were highly consistent with the primary analysis for both outcomes[18].

Table 2. Primary endpoint results from the EXIST-3 study

	Placebo (n=119)	everolimus (low) (n=117)	everolimus (high) (n=130)
Reduction of at least 50% in number of seizures from baseline			
Percentage	15.1 (n=18)	28.2 (n=33)	40.0 (n=52)
95% CI	9.2 to 22.8	20.3 to 37.3	31.5 to 49.0
p value	-	0.0077	<0.0001
OR	-	2.2	3.9
95% CI	-	1.2 to 4.2	2.1 to 7.3
Median percentage reduction in seizure frequency from baseline			
Median percentage reduction	14.9	29.3	39.6
95% CI	0.1 to 21.7	18.8 to 41.9	35.0 to 48.7
p value	-	0.0028	<0.0001
CI: confidence interval; OR: odds ratio.			

Key secondary efficacy endpoints were also found to be consistent with the primary outcomes. Greater response rates (proportion of patients with ≥ 25% reduction from baseline) and seizure free rates (patients remaining seizure free during the maintenance period) were seen in everolimus groups, especially the high-exposure group, compared to placebo group.

Table 3: Selected secondary endpoint results from the EXIST-3 study.

	Placebo (n=119)	everolimus (low) (n=117)	everolimus (high) (n=130)
Proportion of patients achieving at least 25% reduction in seizures	37.8% (n=45)	52.1% (n=61)	70.0% (n=91)
Seizure-free rate (patients remaining seizure free during the maintenance period)	0.8% (n=1)	5.1% (n=6)	3.8% (n=5)
Median number of seizure free days per 28 days (change from baseline)	0.5	2	4

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.

Health-related Quality of Life (HRQoL) was assessed using three age-specific instruments with varying levels of completion rates: QOLCE for children ≤ 10 years of age (administered to caregivers rather than patients) (84%), QOLIE-AD-48 for adolescents 11 – 17 years of age (35%) and QOLIE-31-P for adults ≥ 18 years of age (49%) (see Glossary). These did not identify any significant differences between groups.

3.1.1 EXIST-3 open label extension

Nearly 99% (361/366) of patients entered the extension phase[19]. Data were available for 298 and 163 patients at 1 and 2 years, respectively. This phase was designed to target similar trough concentrations (i.e. 6-10 ng/mL) across the three study arms during the first eight weeks. Afterwards trough concentrations could be titrated according to clinical response within the range of 3-15 ng/m. Response rates were 46.6% (95% CI, 40.9–52.5) at 1 year and 57.7% (95% CI, 49.7–65.4) at 2 years of everolimus exposure. Consistent with these results, the median percentage reduction in weekly seizure frequency improved over time: to 46.7% at 1 year, and to 56.9% at 2 years of everolimus exposure[19].

The greatest benefit was observed in patients initially randomised to high exposure everolimus[19]. The likelihood of observing a 50% of reduction in seizure frequency (calculated during a 12-week period) 1 year after the start of everolimus was 45% in patients who transitioned from placebo to everolimus in the extension phase, 55% in low exposure everolimus, and 70% in the high exposure everolimus group. Fifty percent of patients experienced a persistent response and 59% of these had persistent responses lasting for ≥48 weeks[19].

3.2 Comparative safety

In the double-blind phase of the EXIST-3 study, the majority (>90%) of patients receiving everolimus experienced at least one adverse event, compared to 77.3% of placebo patients[18]. The incidence of serious adverse events was 2.5% in the placebo group, 13.7% in the low exposure group, and 13.8% in the high exposure group. The most common all cause adverse events occurring in either of the everolimus groups (> 15%) during the core phase included stomatitis, diarrhoea, nasopharyngitis, pyrexia, and upper respiratory tract infection[18].

In line with the core phase of the pivotal study (EXIST-3), the most frequent treatment-related adverse events reported in the extension study (up to 2 years) were stomatitis (33.5%), mouth ulceration (26.0%), diarrhoea (10.5%), aphthous ulcer (10.2%), and pyrexia (10.2%)[19]. Serious adverse events were reported in 33.2% of patients, the most frequent being pneumonia (9.1%), seizure (4.2%), and status epilepticus (3.6%).

Adverse events led to treatment discontinuation in 47 patients (13%), primarily because of pneumonia (1.7%) and stomatitis (1.4%). The occurrence of adverse events did not increase over time (≤6 months, 77.8%; >6–12 months, 46.2%; second year, 45.5%)[19].

Two deaths in paediatric patients were suspected to be treatment-related (from pneumonia and septic shock); one during the extension phase and one shortly after the extension phase data cut-off date[19].

The Committee for Human Medicinal Products (CHMP) concluded that results of EXIST-3 were consistent with the already known safety profile of everolimus in TSC patients. CHMP considered everolimus well tolerated and adverse events generally manageable[2].

3.3 Ongoing studies

One clinical trial with everolimus is currently being conducted: A roll-over study (NCT02962414) is assessing long term safety of patients who have completed the EXIST-3 study and who are benefitting from continued treatment. It is expected to complete data collection in 2027.

3.4 AWTTC critique

- Everolimus is currently the only licensed treatment for TSC seizures in the UK and is the only medication with phase III trial data specifically for TSC.
- The trial population included the population covered by the marketing authorisation with respect to seizure burden and prior AED use at baseline. Data on antiepileptic therapy prior to baseline showed that patients were heavily pre-treated and highly refractory with 48.6% of patients having failed ≥ 6 AEDs prior to study[2]. AWTTC-sought expert opinion confirm the study population is representative of patients found in Welsh clinical practice.
- The majority of study subjects were children or adolescents (>80%). The youngest subject included in the study was 2 years old, the oldest 56 years[2].
- Patients were excluded if they had an episode of status epilepticus within one year before the study meaning that some of the relevant patient population may have been excluded.
- Almost 60% of patients randomized to the high-exposure group were below the lower limit of the target C_{min} range (9 ng/mL) after the 18 weeks of exposure to everolimus during the core phase. However, the range of trough concentrations achieved in the study population was thought adequately broad to permit a robust determination of the everolimus exposure-response relationship[18].
- Primary outcomes were from the end of the 12-week maintenance period of the core phase of the study. This is a relatively short period of time considering patients may require lifelong treatment. There are long-term results for up to two years from the extension study. Preliminary data derived from the extension study indicate the treatment effect observed for everolimus during the core maintenance phase of the study is maintained. However, results after 54 weeks should be viewed with caution due to small sample sizes (only including patients that did not discontinue everolimus) and large 95% confidence intervals.
- The safety findings from the core phase and the extension phase were broadly in line with the known safety profile of everolimus in TSC patients.
- The most frequently reported adverse events for everolimus were generally non-overlapping with adverse events observed with AEDs, which may make the tolerability of everolimus in combination with AEDs more acceptable[18].
- Everolimus is administered orally which allows administration at home by patients or carers. It is a dispersible tablet which may be beneficial for patients who have difficulty swallowing tablets. Everolimus requires dose titration according to blood levels and close monitoring for potential adverse effects and this may impact the patient, carers and healthcare services (may require frequent hospital visits) until therapeutic levels are reached.
- Everolimus initiated for the treatment of seizures could be expected to improve other TSC manifestations for which it is also indicated (subependymal giant cell astrocytoma (SEGA) and renal angiomyolipoma). However, it should be noted that the exposure-response relationship differs among the different indications[18].
- There were marginal changes for health-related quality of life in all three treatment arms. The EMA note 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.
- Neurocognitive, neurobehavioural and neurodevelopmental outcomes were planned to be collected in EXIST-3 however no results for these outcomes were presented. It is possible that substantial intellectual disability in the

study population impacted the ability of patients / investigators to complete these questionnaires and the patient-administered QOLIE-AD-48 and QOLIE-31-P instruments[20].

4.0 COST-EFFECTIVENESS

4.1 Context

The company submission includes a cost-utility analysis (CUA) comparing dispersible everolimus tablets (2mg, 3mg, 5mg) in combination with best supportive care (BSC) with BSC as a treatment for patients with refractory partial-onset seizures (POS), with or without secondary generalisation, associated with tuberous sclerosis complex (TSC). BSC is assumed to consist of symptomatic treatment with AEDs.

The CUA takes the form of a decision tree followed by a Markov state-transition model comprising a series of 12-week cycles. The model adopts a lifetime time horizon extended to 100 years and an NHS/Personal and Social Services perspective. Costs and outcomes are discounted at 3.5%. The submission incorporates a simple Patient Access Scheme discount of [commercial in confidence figure removed] on list price. The decision tree is used to establish initial response to treatment. Treatment response is defined as ≥50% reduction in the mean seizure frequency, in line with the primary endpoint of the EXIST-3 trial[18].

Six response states are used as the starting distribution of patients in the Markov model: <0% reduction (i.e. exacerbation of seizures), 0 to <25% reduction, 25 to <50% reduction, 50 to <75% reduction, 75 to <100% reduction, and 100% reduction (seizure-free). Patient response to treatment is assessed at each cycle, with patients able to maintain, lose or improve levels of response. On loss of treatment response, patients are conservatively assumed to return to baseline (uncontrolled seizures with 0% mean seizure reduction) in the next cycle of the model. Patients can transition between these states for up to four years, after which they are assumed to maintain their response level. Only patients who achieved a treatment response are modelled to continue treatment with everolimus. Patients can also discontinue as a result of unacceptable adverse events. On discontinuation, patients are assumed to receive BSC only with no further benefit in terms of seizure control. Patients can transition to death from any health state.

The efficacy data used to inform the decision tree and transition probabilities for patients receiving everolimus plus BSC are derived from the EXIST-3 trial[18]. However, BSC transition probabilities are based on a retrospective study of TSC patients treated with clobazam[21], because patients in the placebo arm of EXIST-3 received open-label everolimus in the extension phase of the trial. The probability of experiencing Grade 3 and 4 treatment-related adverse events is taken from the pivotal trial[18]. The mortality ratio is informed by comparisons of National life tables for Scotland and Kaplan-Meier curves for TSC-related mortality[22].

The model includes medicine acquisition costs, epilepsy monitoring and management costs, and adverse events costs. Also included are costs associated with TSC-related neuropsychiatric comorbidities and other clinical manifestations of TSC. The mean dose for everolimus, 7.2 mg/m^2 once daily, and other AEDs is pooled from the pivotal EXIST-3 trial[18]. PSSRU unit costs are used for monitoring[23]. Epilepsy management costs are informed by the UK CPRD database[24] and are adjusted in the model according to age, level of response, seizure type and seizure frequency. These adjustments are guided by the literature[25-27]. Standard sources have been used for

costing the management of epilepsy and adverse events[23,28]. Costs associated with TSC-related neuropsychiatric comorbidities are sourced from a survey of older adults with intellectual disability conducted in London, and clinical guidelines for generalised anxiety disorder and bipolar disorder[23,29-31]. Clinical manifestations of TSC costs are also sourced from the literature and guidelines[23,29,31-33].

Health outcomes are accrued in all six treatment-response-related health states and are stratified for seizure type. Health Utilities Index (HUI) data are sourced from a sub-study of a Dutch medical chart review conducted in 2012[34]. The original HUI data are stratified by seizure type and number of AEDs. In order to derive utilities corresponding to the response states characterised in the model, a number of assumptions are applied, including: use of the number of AEDs as a proxy for seizure control; and applying the 'absence' seizure type utility value to focal seizures, and the 'tonic-clonic' utility value to generalised or secondary generalised seizures. Utility values in the base case are not restricted to effects on epilepsy alone, but also included are utility decrements for TSC-associated clinical manifestations, specifically: patients with SEGA who received surgery (0.09), patients with renal angiomyolipoma growth >3.5 cm (0.08), and the presence of facial angiofibromas (FA) (0.08).

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results. The parameters tested, among others, included: distributions of patients in epilepsy control/response categories, adverse event discontinuation, proportions for seizure type, transition probabilities and utility values. Scenario analyses also explore: alternative time horizons; using an alternative source of patient baseline characteristic inputs (TOSCA registry rather than EXIST-3); excluding the effects of everolimus on the neuropsychiatric comorbidities and other clinical manifestations of TSC; exploring alternative assumptions around loss of response; alternative transitions between response categories in the long term.

4.2 Results

The results of the base case are detailed in Table 4. When compared with BSC, the incremental cost-effectiveness ratio (ICER) generated is [commercial in confidence figure removed] per quality-adjusted life-year (QALY) gained. The main cost differences are attributable to the acquisition cost of everolimus. The incremental QALY gains are attributable to quality of life gains, predominantly improvements in epilepsy manifestation of TSC (incremental QALY gain of 0.814).

Table 4. Results of the base case analysis

	Everolimus (Votubia®)	Comparator AEDs	Difference
Medicine acquisition costs (including other drug costs)	¶¶	£95,620	¶¶
Procedures	£65,627	£65,702	**-£75**
Adverse event management	£916	£871	**£45**
Monitoring costs	£54,472	£55,387	**-£915**
Epilepsy management	£129,014	£126,718	**£2,296**
Comorbidities management costs	£109,611	£113,856	**-£4,245**
SEGA costs	£5,797	£9,922	**-£4,125**
Renal angiomyolipoma costs	£1,286	£3,149	**-£1,863**
FA costs	£2,831	£2,901	**-£70**
Total costs	¶¶	£474,126	¶¶
Total life-years	25.271	25.271	**0**
Total QALYs	6.808	5.925	**0.883**
ICER (£/QALY gained)*	¶¶		

¶¶: commercial in confidence figure removed

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
* does not compute due to rounding

The results of the univariate sensitivity analysis show that the ICER is most sensitive to: the distribution of patients in epilepsy control categories (in both the treatment arm and the BSC arm); the proportion of patients with secondary generalised convulsive seizures at 66 weeks; the prevalence of SEGA across different age groups; the probability of discontinuation with everolimus due to adverse events; and mean seizure frequency reduction <0% (i.e. exacerbations) for BSC. Variations in most of these parameter estimates produce ICERs exceeding the base case estimate, with four exceeding £40,000 per QALY gained. The results of scenario analysis are included in Table 5.

Probabilistic sensitivity analyses produced an ICER of [commercial in confidence figure removed] per QALY-gained and indicated that everolimus in combination with BSC has a [commercial in confidence figure removed] and [commercial in confidence figure removed] probability of being cost-effective at a threshold of £30,000 and £50,000 per QALY gained, respectively.

Table 5. Results of scenario and sensitivity analyses

Scenarios	ICER	Plausibility
Exclusion of the effects on other TSC manifestations and neuropsychiatric comorbidities	¶¶	This scenario provides a useful insight into the effects of the inclusion of the additional benefits and costs associated with these other manifestations and comorbidities. This scenario provides a more plausible ICER estimate than the company base case. It focuses on seizure benefits only, thereby drawing a boundary around the analysis to focus on the indication being appraised.
Alternative time horizons a) 10 years b) 20 years	**a)** ¶¶ **b)** ¶¶	These scenarios are unlikely to capture all of the costs associated with this patient group. However, they reduce the uncertainty associated with combining extrapolated short term open label extension trial data, with the assumption that after 4 years patients maintain their response level and an extended time horizon of 100 years. These scenarios additionally provide useful insight into the length of time required to accrue QALY gains.
Baseline characteristics taken from TOSCA registry	¶¶	This scenario offers a useful alternative to explore the effects of alternative baselines characteristics.
Alternative state for loss of response: Remain in non-responder state (i.e. 0 to <25% reduction, or 25 to <50% reduction)	¶¶	This scenario provides a less conservative approach to lack of response (in base case return to baseline with a mean seizure reduction of 0%)
¶¶: commercial in confidence figure removed		

4.3 AWTTC critique

The company submission does not include an executable cost-utility model. This prohibits: a comprehensive critique of the model and the results produced, the ability to validate model results and assess the impact on the ICER of alternative assumptions and scenarios, and the opportunity to conduct additional AWTTC explorations of uncertainty. The cost-effectiveness estimates are therefore subject to considerable uncertainty and are restricted to company conducted analyses that cannot be verified.

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed account of the data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model in most instances.
- A range of sensitivity and scenario analyses have been conducted by the company.

Limitations:

- The ICER is highly influenced by the inclusion of benefits to patients other than those targeted by the indication under review. It is questionable whether these wider benefits should be included in the base case. When removed, the ICER increases significantly, driven by a higher incremental cost due to the exclusion of TSC related costs in the BSC arm and the loss of TSC related benefits in the everolimus arm (see Table 5).

- The long-term benefits of treatment with everolimus are extrapolated over the lifetime time horizon of 100 years using data captured in week 66. Extrapolation over this extended period naturally introduces uncertainty. Combined with the assumption that patients maintain their response level after 4 years, this introduces considerable uncertainty in the ICER estimates.
- Given the low completion rates of the health-related quality of life questionnaires used in the pivotal study, together with the lack of reliable and validated algorithms to map them to the EQ-5D, the utilities used in the model are based on a Dutch chart review[34]. The robustness of the utilities applied is uncertain, as is how representative these values are of the Welsh population. These factors contribute to uncertainty around the utility values used in the analysis.
- Transition probabilities for BSC are not based on EXIST-3 data as a consequence of the extension study design. Instead they are taken from a retrospective analysis of TSC patients treated with clobazam[21]. The company identify the study population as being similar to those in the EXIST-3 study, due to them being heavily pre-treated with AEDs and typically receiving between one and three concomitant AEDs. However, there is no detailed assessment of heterogeneity between the study samples; or details of how any potential differences in baseline characteristics have been adjusted for. The calculations to explain how the response categories were mapped from a frequency of <50%, >50% and >90% to the response categories defining the health states in the model cannot be verified and therefore the robustness of the utilities applied is uncertain.
- It is uncertain whether the AED medicines used for BSC in the model are representative of the BSC medicines used in Wales today in this patient group. This has implications for both the costs and effects associated with BSC in the model. However, AWTTC-sought clinical expert opinion suggests that the AEDs currently used in Welsh patients are similar to those used in the model.
- The resource use captured in the model for the management of epilepsy, TSC-related neuropsychiatric comorbidities and other clinical manifestations may not be reflective of current practices and costs in Wales, given the age of the source studies and that unit costs are taken from 2016. AWTTC checks reveal some notable changes to BSC medicine costs. Combined, these factors introduce uncertainty and have implications for the cost comparisons used in producing ICER estimates.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by All Wales Therapeutics and Toxicology Centre (AWTTC) did not identify any research studies relevant to the cost-effectiveness of Votubia® in the population of interest.

5.0 BUDGET IMPACT

5.1 Context and methods

The analyses estimate that there will be 35 people with refractory POS associated with TSC in year 1, increasing to 39 in year 5. These estimates have been derived using: Welsh Government age-based population and live birth statistics[35,36], TSC prevalence information from Orphanet[1]*, TSC incidence from an epidemiology study reported on in 1991[37], and refractory POS estimates informed by the international TSC disease registry (TOSCA)[3].

*AWTTC was unable to validate the Orphanet prevalence figure provided by the company

Based on company-sought clinical expert opinion, it is assumed that 25% of eligible patients will receive everolimus in Year 1, increasing to 45% in Year 5.

A discontinuation rate for everolimus of 16.57%, informed by the pivotal study[18], is also applied to estimate the number of people likely to be prescribed everolimus in Wales for the indication covered in the submission. The PAS price for everolimus is used to estimate medicine acquisition costs. Dosing for everolimus is based on a combination of: pivotal trial data[18]; an assumption that 50% of patients will receive a higher dose to attain a higher trough concentration to obtain optimal efficacy; and an age distribution informed by the TOSCA registry[3]. The cost of BSC medicines is not included in the analysis.

5.2 Results

The budget impact is presented in Table 6. The company estimates that introducing everolimus would lead to an overall cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The company has not carried out any additional sensitivity analyses.

Table 6. Company-reported costs associated with use of everolimus for the treatment of refractory POS associated with TSC

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (all licensed indications*)	65	66	67	68	69
Sub-population of eligible patients (i.e. patients with refractory POS associated with TSC)	35	36	37	38	39
Uptake of new medicine (%)	25%	30%	35%	40%	45%
Number of patients receiving new medicine allowing for discontinuations	8	10	11	13	15
Medicine acquisition costs in a market without new medicine	0	0	0	0	0
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶: commercial in confidence figure removed

* Only required if a case is being made for an orphan/ultra-orphan treatment or a medicine developed specifically for rare diseases

5.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact. Discontinuation is also factored into the calculations.
- The analysis uses a prevalence of 1 in 18,150 for TSC. When orphan status for Votubia® was granted by the EMA, the estimated prevalence of people with TSC was 1 in 10,000 in the European Union (EU)[38]. Current Orphanet estimates lie between 1 in 10,000 and 5 in 10,000[39]. If this were the case in Wales, the reported BI predictions would underestimate eligible patient numbers and the additional

costs associated with the introduction of everolimus. However, AWTTC verification of patient numbers with the specialist centre in Wales supports the company estimate of prevalence.

- It is uncertain whether the company-sought estimates for everolimus uptake are representative of the anticipated use in Wales. The specialist centre in Wales predicts use in 12 to 15 patients per annum, which equates to a cost of £296,298 and £370,373 per annum. Additional costs could therefore be higher than predicted.
- It is uncertain whether the patient distribution and dosing assumptions used in the analysis are representative of the Welsh population in terms of age, body surface area and the proportion of patients receiving high and low trough treatment regimens. This has implications for dosing, and the additional medicine acquisition costs consequently apportioned to the introduction of everolimus. Additionally, AWTTC are unable to verify the calculations for Age & Sex Proportional Average Dose due to lack of transparency in methods.
- The budget impact considerations are limited to the acquisition costs associated with everolimus only. This approach does not provide insight into the magnitude of the additional costs associated with everolimus within the wider context of the usual BSC costs associated with treating this patient population. Other resource use is also not included (e.g. monitoring costs and costs associated with adverse events).
- The lack of sensitivity analyses prevents useful exploration of the impact of uncertainty around model assumptions and inputs (e.g. alternative dosing and uptake assumptions).

6.0 ADDITIONAL FACTORS TO CONSIDER

6.2 Medicines developed to treat rare diseases

The applicant company suggests everolimus should be considered as an ultra-orphan medicine. In addition to the indication included in this submission, the dispersible formulation of everolimus is licensed for treatment of adult and paediatric patients with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery. The tablet formulation of everolimus includes adult patients with renal angiomyolipoma associated with TSC who are at risk of complications but who do not require immediate surgery.

The company estimates that: 39 patients will be eligible for treatment with everolimus in year 5, for the indication included in this submission; 19 patients will be eligible for the SEGA related indication per annum[40], and; 10 patients will be eligible for the renal angiomyolipoma related indication per annum[41,42]. When combined, these patient numbers exceed the threshold for everolimus to be considered an ultra-orphan medicine. However, AWTTC-sought clinical expert opinion suggests that 16 patients will likely receive everolimus for the SEGA-related indication; in addition to 3 patients for the renal angiomyolipoma indication.

AWTTC does consider everolimus eligible to be appraised as an orphan medicine, however it is questionable whether it is eligible to be appraised as an ultra-orphan medicine. The full population of the licensed indication does not exceed the threshold ≤ of 1 in 2,000 people in Wales (or the UK), but may exceed the threshold of ≤ 1 in 50,000 people in Wales (or the UK). There is notable uncertainty in relation to the number of patients with: SEGA associated with TSC who require therapeutic

intervention but are not amenable to surgery; and renal angiomyolipoma associated with TSC who are at risk of complications but who do not require immediate surgery. It is plausible that the population for all licensed indications exceeds the threshold for everolimus to be considered an ultra-orphan medicine.

Table 7. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
Severity of the disease	TSC is an autosomal dominant, multisystem disorder characterised by the formation of benign, non-invasive lesions which can form throughout the body, leading to diverse clinical manifestations. However, the majority of TSC morbidity and mortality arises from the neurological and neuropsychiatric manifestations, which often prove the most challenging to treat. Epilepsy is the most common neurological symptom affecting the majority of people with TSC[3]. Seizures in patients who develop TSC-associated epilepsy in early childhood typically become increasingly frequent and severe over time. Uncontrolled epilepsy is believed to be a contributing factor to learning disabilities in people living with TSC. TSC patients with refractory POS may experience as many as thirty seizures within the space of 28 days[18]. Furthermore, patients with TSC-associated epilepsy may develop significant comorbidities, such as autism spectrum disorders (13–30% of patients) and cognitive impairment/delay (62–80%), which may have long-term detrimental effects[43].
Unmet need	There is no TSC specific anti-epilepsy medication so anti-epileptic drugs (AEDs), either alone or in combination with other AEDs, are the most common treatment in UK clinical practice[9]. At least one-third of patients are known to have refractory epilepsy with their seizures not successfully controlled by existing AEDs[3,44]. There is thus a substantial unmet need for new therapeutic approaches for the treatment of epilepsy in TSC, to improve seizure control, cognitive function, and patient quality of life.
Innovative nature of the medicine	Everolimus acts by blocking the over-activation of a specific enzyme which is thought to be the cause of seizures in people with TSC. Unlike AEDS which treat only the symptoms, everolimus targets the underlying cause of the seizures[2]. It is the only licensed medicines available for the treatment of refractory seizures associated with TSC. It is also used for the treatment of other clinical manifestations of TSC and so a patient prescribed everolimus for seizures may also experience beneficial effects on these manifestations, thus improving their overall health and quality of life[18].
Societal impact on non-health benefits that may not adequately be captured in the QALY	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[14]. Everolimus has the potential to decrease the number, frequency and severity of seizures enabling a better quality of life for patients and their families. In addition, the Tuberous Sclerosis Association have stated that there is a lower risk of serious co-morbidity and mortality (such as sudden unexpected death in epilepsy (SUDEP) if everolimus can provide better seizure control.
Does the medicine cure or reverse rather than stabilise the condition?	No

Does the medicine bridge a gap to a definitive therapy?	Gene therapy is currently unavailable for TSC. Until such therapy can be offered, everolimus offers a potential treatment for people with TSC whose seizures remain uncontrolled by currently available AEDs.
AEDs: anti-epileptic drugs; AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; NMG: New Medicines Group; TSC: tuberous sclerosis complex	

GLOSSARY

Quality of Life Childhood Epilepsy (QOLCE): for children ≤ 10 years of age (administered to parents/caregivers rather than patients)

Quality of Life in Epilepsy for Adolescents-48 (QOLIE-AD-48): for adolescents 11 – 17 years of age (administered to patients however assistance from parent or caregiver was permitted if patient was either a) unable to sign the instrument, or b) capable of indicating the correct response but physically incapable of marking the score sheet).

Quality of Life in Epilepsy-31-Problems (QOLIE-31-P): for adults ≥ 18 years of age (administered to patients however assistance from parent or caregiver was permitted if patient was either a) unable to sign the instrument, or b) capable of indicating the correct response but physically incapable of marking the score sheet).

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