AWMSG Secretariat Assessment Report
Cannabidiol (Epidyolex®) 100 mg/ml oral solution

1.0 KEY FACTS

Assessment details	Cannabidiol (Epidyolex®) for adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older.
Current clinical practice	Current management consists of anti-epileptic drugs (AEDs), either alone or in combination with other AEDs, and non-pharmacological interventions such as epilepsy surgery, vagus nerve stimulation (VNS) and ketogenic diet. Everolimus is the only other licensed adjunctive therapy specifically for TSC-associated seizures. AWTTC-sought clinical expert opinion indicates a substantial unmet need for the treatment of drug-resistant seizures associated with TSC. Cannabidiol offers an additional treatment option for this patient population. Welsh clinical experts confirm cannabidiol would be used before everolimus in the treatment pathway for TSC-associated epilepsy and as an add-on treatment option once two different AEDs have failed to achieve adequate seizure control.
Clinical effectiveness	The main evidence comes from a phase III double-blind study (GWPCARE6) and its respective open label extension phase, comparing cannabidiol oral solution (25 or 50 mg/kg/day) alongside usual care with placebo plus usual care. Usual care consisted of treatment with between one and five AEDs (mean = 3 AEDs). Results from the pivotal study demonstrated cannabidiol significantly reduced TSC-associated seizures at the end of the16-week treatment period compared with placebo. This was supported by the key secondary outcome, the proportion of patients with at least a 50% reduction in TSC-associated seizure frequency. Both doses showed comparable efficacy, but the higher dose was associated with an increased rate of treatment related adverse events. Therefore, a maximum cannabidiol dose of 25 mg/kg/day is recommended for the indication under consideration. Interim results from the open-label extension study demonstrates cannabidiol maintains its efficacy in controlling seizures at 72 weeks of treatment.
Cost-effectiveness	A cost-utility analysis compares cannabidiol oral solution plus usual care (defined as a combination of AEDs) with usual care alone for adjunctive treatment of seizures associated with TSC for patients 2 years of age and older.

	The company base case suggests that cannabidiol plus usual care is [commercial in confidence figures removed] more costly and produces an additional [commercial in confidence figures removed] quality-adjusted life-years (QALYs) compared to usual care alone over the 100-year lifetime horizon with an ICER of [commercial in confidence figures removed] per QALY gained based on a Patient Access Scheme price. The model structure appears robust to sensitivity and scenario analyses provided by the company, with the most plausible ICER estimates for cannabidiol plus usual care ranging from [commercial in confidence figures removed] per QALY gained. The ICER is most sensitive to the inclusion of caregiver disutility and TSC-associated neuropsychiatric disorders (TAND) costs and utilities, stopping rule assessment rate applied at 6 months for patients with a seizure frequency greater than seven seizures per week, the highest seizure frequency category, followed by the number of caregivers, the patient utility values applied to seizure-free patients, and response rates used to estimate the proportion of patients who benefit from a reduction in TSC-associated neuropsychiatric disorders (TAND) symptoms.
Budget impact	The company estimates that [commercial in confidence figures removed] patients would receive treatment with cannabidiol in Wales in Year 1, increasing to [commercial in confidence figures removed] in Year 5. The company estimates that introducing cannabidiol would lead to an overall cost of [commercial in confidence figures removed] in Year 1, increasing to [commercial in confidence figures removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of usual care. However, as cannabidiol is to be used in addition to usual care, the budget impact presented by the company may underestimate the cost. The budget impact analysis is subject to considerable uncertainty based around the prevalence and incidence values, uptake rates and cost of usual care.
Additional factors to consider	Cannabidiol (Epidyolex®) has been designated as an orphan medicine by the European Medicines Agency. AWTTC considers cannabidiol eligible to be appraised as an orphan medicine.

This assessment report is based on evidence submitted by GW Research Ltd[1] and an evidence search conducted by AWTTC on 17 August 2021.

2.0 BACKGROUND

2.1 Condition and clinical practice

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder caused by a mutation in either the tuberous sclerosis gene 1 (TSC1) or tuberous sclerosis gene 2 (TSC2)[2]. These genes are involved in regulating cell growth and deficiency of either gene causes uncontrolled cell proliferation often leading to the

development of multiple benign tumours in different organs of the body[2]. TSC is characterised by lesions in the brain, kidneys, heart, lungs, eyes and skin which can cause a variety of associated health problems ranging from mild to severe[3]. TSC is associated with neurodevelopmental and neurocognitive disorders, including autism and intellectual disability.

Epileptic seizures are the most common neurological manifestation of TSC, affecting over 80% of patients[4]. The onset of epilepsy often occurs in the first year of life and commonly manifests with focal seizures and infantile spasms although many people develop multiple seizure types. Frequent treatment-resistant seizures are common, and can have a severe negative impact on physical and mental health[1,2]. Uncontrolled epilepsy is among the most common causes of death in TSC as a result of status epilepticus or sudden unexpected death in epilepsy (SUDEP)[1,2].

The goal of treatment is to prevent or reduce the number and frequency of seizures and the cognitive and neuropsychiatric consequences associated with treatment-resistant epilepsy. Early management of seizures also improves long-term intellectual development when treatment provides a prompt response[5]. The most common treatment used in clinical practice is anti-epileptic medications (AEDs), either alone or in combination with other AEDs. Treatment is guided by several factors including patient co-morbidities, concurrent medication and medicine tolerability[5]. Most patients with TSC take between three and five AEDs, although current treatment regimens rarely provide sufficient seizure control and nearly two-thirds of TSC patients develop refractory seizures[2]. Refractory seizures are those which do not respond to anti-epileptic medication: in UK clinical practice, seizures are defined as refractory when two different AEDs have failed to provide seizure control[6,7]. Non-pharmacological treatment options include epilepsy surgery, vagus nerve stimulation and ketogenic diet[2].

The only other licensed adjunctive therapy for TSC-associated seizures is everolimus. In September 2021, the All Wales Medicines Strategy Group (AWMSG) recommended the use of 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[8]. Welsh clinical experts indicate cannabidiol would be used before everolimus in the treatment pathway for TSC-associated epilepsy and is an add-on treatment option once two different AEDs have failed to achieve adequate seizure control[2].

2.2 Medicine

Cannabidiol (Epidyolex®) oral solution is a novel anti-convulsant, plant-derived cannabinoid medicine[1,6,9]. The precise mechanism of action is unknown although it is thought cannabidiol acts on the GPR55 and TRPV1 protein channels and reduces neuronal hyper-excitability in the brain. It may exert a cumulative anti-convulsant effect through modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid 1 (TRPV-1) channels, as well as modulation of adenosine-mediated signalling through inhibition of adenosine cellular uptake via the equilibrative nucleoside transporter 1 (ENT-1) [9,10].

Cannabidiol (Epidyolex®) was granted marketing authorisation by the European Medicines Agency (EMA) in April 2021 and the Medicines and Healthcare products Regulatory Agency (MHRA) in August 2021 for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older[2]. Cannabidiol is an add-on treatment and should be used in combination with other anti-epileptic medications[10].

The recommended starting dose of cannabidiol is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a dose of 5 mg/kg twice daily (10 mg/kg/day) and the clinical response and tolerability should be assessed. The dose can be further increased if needed in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 12.5 mg/kg twice daily (25 mg/kg/day)[10]. If cannabidiol has to be discontinued, the dose should be decreased gradually[10].

The company-proposed stopping criteria is based on recommendations in clinical practice[1]. The frequency of TSC-related seizures should be assessed every six months, and cannabidiol should be stopped if the frequency has not fallen by at least 30% compared with the six months before starting treatment[10].

2.3 Comparators

The comparator included in the company submission is established clinical management ('usual-care'), which includes combinations of different anti-epileptic medications[1].

2.4 Guidance and related advice

- NICE clinical guideline 137 - Epilepsies: diagnosis and management (2012, updated 2021)[5]
- UK TSC guidelines (2019)[11]
- European Consensus Meeting, Management of epilepsy associated with tuberous sclerosis complex: updated clinical recommendations (2018)[12]
- International TSC consensus Conference (2012)[13]

2.5 Prescribing and supply

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

3.0 CLINICAL EFFECTIVENESS

The company's submission includes evidence from a phase III, double-blind, randomised controlled study (GWPCARE6) and its respective open label extension study, both summarised below.

3.1 GWPCARE6

This was a randomized, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of 25 mg/kg/day and 50 mg/kg/day cannabidiol dosages given as add-on therapy. The study enrolled patients aged 1 to 56 years (mean age 14 years) with a confirmed diagnosis of TSC and medication-resistant epilepsy[14].

Eligible patients had at least eight seizures during the four-week baseline period, with at least one seizure in at least three of the four weeks. All patients but one were receiving between one and five AEDs (mean AEDs = 3) at a stable dose for at least four weeks before screening[2,14]. The most common AEDs were valproate (44.6%), vigabatrin (33.0%) levetiracetam (29.0%) and clobazam (27.2%)[14]. This AED treatment, defined as 'usual care', was continued during the trial alongside the study medication (cannabidiol or placebo). Patients taking everolimus were excluded from the study[2,14].

Patients (n = 224) were randomly assigned in a 2:2:1:1 ratio to one of four treatment arms to receive:

- Cannabidiol 25 mg/kg/day oral solution plus usual-care; or

- Cannabidiol 50 mg/kg/day oral solution plus usual-care; or
- Placebo 25 mg/kg/day dose-volume equivalent plus usual-care; or
- Placebo 50 mg/kg/day dose-volume equivalent plus usual-care.

Randomisation was stratified by age subgroup (1–6 years, 7–11 years, 12–17 years, and 18–65 years). For the first four weeks of the study the dose was slowly titrated to attain the assigned target dose and this was maintained for the following 12 weeks. An interactive voice response system was used daily to record information on seizures. Dose escalation for each patient was subject to the investigator's assessment of safety and tolerability. The use of rescue medication to provide additional seizure control was allowed when necessary.

Following completion of the 12-week maintenance period, patients had the option to enter the open-label extension study and continue to receive cannabidiol treatment. Patients who discontinued before the end of the treatment phase completed a 10-day taper period (down-titrating 10% per day for 10 days)[2,14].

The primary endpoint was the change from baseline in number of TSC-associated seizures (see Glossary) for cannabidiol compared to placebo during the 16-week treatment period (titration plus maintenance periods). This was assessed in the intention-to-treat population, which comprised all randomised patients who received study drug and had post-baseline efficacy assessment[2]. The study met its primary endpoint in both cannabidiol treatment arms (see Table 1), demonstrating that cannabidiol had a statistically significant effect in the reduction of TSC-associated seizure frequency from baseline (25 mg/kg/day: 30.1%; 50 mg/kg/day: 28.5%) compared to placebo at the end of the 16-week treatment period[14]. Results were consistent across all age subgroups[2,14].

Table 1. Primary endpoint results from GWPCARE6 study[2,14].

	Cannabidiol 25 mg/kg/day (n = 75)	Cannabidiol 50 mg/kg/day (n = 73)	Placebo (n = 76)
Reduction from baseline in TSC-associated seizure frequency			
Percentage	48.6	47.5	26.5
95% CI	40.4 to 55.8	39.0 to 54.8	14.9 to 36.5
Reduction from baseline in TSC-associated seizure frequency compared to placebo			
Percentage	30.1	28.5	-
95% CI	13.9 to 43.3	11.9 to 42.0	-
p value	0.0009	0.002	-
CI; confidence interval			

Key secondary outcomes included the proportion of patients considered treatment responders, defined as those with a ≥ 50% reduction from baseline in TSC-associated seizure frequency; percentage change from baseline in total seizures and change in subject or caregiver global impression (S/CGIC) scores (see Glossary) at the last visit[2]. Although the 50% responder analysis (considered the most important secondary outcome) did not reach statistical significance, all secondary outcome results were considered supportive of the primary endpoint (see Table 2)[1,2,14].

Table 2. Selected secondary endpoint results from the GWPCARE6 study[2,14].

	Cannabidiol 25 mg/kg/day (n = 75)	Cannabidiol 50 mg/kg/day (n = 73)	Placebo (n = 76)
Patients with a ≥ 50% reduction from baseline in TSC-associated seizure frequency			
Percentage p value OR	36.0 0.0692* 1.95	39.7 0.0245 2.29	22.3
Patients with a ≥ 75% reduction from baseline in TSC-associated seizure frequency			
Percentage	16.0	17.8	0
Reduction from baseline in total seizures			
Percentage	48.1	47.6	26.9
Change from baseline in seizure-free days			
LS mean (days)	6.23	5.57	3.41
Change in S/CGIC scores at the end of treatment period compared to last visit			
Percentage improvement	68.6 (n = 48/70)	62.3 (n = 43/69)	39.5 (n = 30/76)

OR; odds ratio
LS: least square
*The OR for achieving a ≥ 50% reduction in TSC associated seizure frequency did not reach statistical significance and therefore the hierarchical testing ended.

Subgroup analysis of patients receiving concomitant clobazam showed a 61.1% reduction from baseline in TSC-associated seizure frequency for the cannabidiol 25 mg/kg/day treatment group compared to a 27.1% reduction for the placebo group. This compares to a reduction of 44.4% in the 25 mg/kg/day cannabidiol group and 26.2% in the placebo group for patients not receiving concomitant clobazam[2,10].

Rescue medication use increased in all treatment groups although the change from baseline in the number of days of reported rescue medication use was numerically in favour for the cannabidiol treatment group compared to placebo (25 mg/kg/day: 16 days vs. placebo: 20 days)[2].

3.2 Open-Label Extension study

Of the 201 patients who completed the GWPCARE6 study, 99.0% (n = 199) were enrolled into the open-label, two year extension (OLE) study[15]. The primary endpoint of the OLE is safety and tolerability with key secondary endpoints including percentage reduction in TSC-associated seizures, responder rates, and quality of life[1]. Interim data until week 72 has been published[15] with the final results expected to be available in early 2022[1].

All patients were transitioned to 25 mg/kg/day, followed by a three-week dose optimisation titration period (up to 50 mg/kg/day). Most patients (n = 150) were in the 20-30 mg/kg/day group with the remaining patients in either the 20 mg/kg/day group (n = 19) or the > 30 mg/kg/day group (n = 30)[2].

Interim analysis to week 72 showed 12% of patients had completed the study, 57% were ongoing and 31% had been withdrawn[15]. Seizure reductions (measured across 12-week windows) were 54%–80% for patients with a modal dose ≤ 25 mg/kg/day (n = 145). The ≥ 50%, ≥ 75%, and 100% responder rates were maintained up to 72 weeks, ranging from 52%–63%, 29%–51%, and 6%–19% respectively[15]. More than 85% of patients/caregivers reported an improvement in the patient's overall condition on the S/CGIC scale at the 26 and 52-week visits[1].

3.3 Comparative safety

The evaluation of the safety and tolerability of cannabidiol is based on data from the GWPCARE6 and OLE studies plus supportive data from expanded access and compassionate use programmes[1]. Data from the pivotal study showed that the majority of patients experienced at least one treatment emergent adverse event (TEAE) across both treatment and placebo groups (cannabidiol 25 mg/kg/day: 93.3%, cannabidiol 50 mg/kg/day: 100% and placebo: 94.7%); 88% were reported as mild or moderate[2]. More patients experienced TEAEs using concomitant clobazam across all treatment arms[2].

The most frequently reported TEAEs for cannabidiol use included diarrhoea, decreased appetite, pyrexia, vomiting, and somnolence[2]. There was a dose-related increase in the incidences of TEAEs[2]. The incidence of serious TEAEs related to cannabidiol treatment was eight patients (10.7%) in the 25mg/kg/day group and six patients (8.2%) in the 50 mg/kg/day group; liver enzyme level elevations were the most frequent serious adverse event[2]. The observations concerning liver safety are consistent with previously approved cannabidiol indications and the Summary of Product Characteristics outlines precautions and additional monitoring[10].

Treatment discontinuation due to an adverse event was more common in the cannabidiol treatment arms (25 mg/kg/day: n = 8 [10.7%], 50 mg/kg/day: n = 10 [13.7%]) compared to placebo (n = 2 [2.6%]); the most common TEAEs leading to discontinuation were rash, liver enzyme level elevation, somnolence and urticaria[2]. Concomitant use of more than four AEDs was associated with increased incidences of TEAEs leading to discontinuation[2].

In the pooled analysis, six TSC patients had at least one significant adverse cardiovascular event considered related to cannabidiol use compared to none in the placebo group and which resulted in discontinuation of treatment[2]. Cardiovascular monitoring is standard of care for TSC patients and additional data on any cannabidiol effect will be provided through a QTc trial[2,10].

The Committee for Medicinal Products for Human Use (CHMP) stated the safety profile could not be established for patients aged less than 2 years. It also highlighted that the number of cannabidiol dose reductions and discontinuations due to TEAEs were higher in the TSC studies compared with previous studies for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome[16,17]. The TSC studies included patients on higher cannabidiol doses (up to 50 mg/kg/day) and due to safety and tolerability concerns, the maximum recommended dose is 25 mg/kg/day[2,10].

3.4 AWTTC critique

- There is a substantial unmet need for the treatment of TSC-related epilepsy. Everolimus is currently the only other medicine specifically licensed in the UK for the adjunctive treatment of seizures associated with TSC. Cannabidiol provides an additional treatment option for patients.
- The indication does not specify use in epilepsy inadequately controlled on anti-epileptic drugs (AEDs); although the applicant company and Welsh clinical experts indicate place in therapy is likely to be in this patient group and after two different AEDs have failed to achieve adequate seizure control. The company advised AWTTC as cannabidiol TSC indication is for adjunctive therapy patients will have already tried and failed to achieve seizure control with other AEDs.
- The company submission includes usual care (defined as a combination of different AEDs), as the only relevant comparator. Welsh clinical experts suggest

this is appropriate given everolimus would be used after cannabidiol in the TSC treatment pathway.

- The GWPCARE6 study consists of a highly refractory population; most patients had used three or more AEDs prior to entering the study[2]. This treatment-resistant population is representative of patients found in Welsh clinical practice. However, it is unclear whether the trial population reflects the place in therapy for cannabidiol use i.e. once two different AEDs have failed to achieve adequate seizure control.
- The primary endpoint demonstrated greater reduction in TSC-associated seizures in the cannabidiol treatment groups and was supported by the key secondary outcome, the proportion of patients with at least a 50% reduction in TSC-associated seizure frequency. Although this did not reach statistical significance, the reduction in seizure frequency was numerically higher in the cannabidiol 25 mg/kg/day treatment group compared to placebo[2].
- As observed in the cannabidiol studies for other indications, a higher efficacy was found with concomitant clobazam treatment, which can be explained by the known pharmacokinetic interaction[2]. However, CHMP noted clobazam is rarely used for the treatment of TSC-associated seizures and has considerable safety issues. The treatment effect of cannabidiol without concomitant clobazam therapy still reached statistical significance and was considered clinically relevant. CHMP suggested the decision to use concomitantly with clobazam should be made individually according to patient need and treatment response[2].
- The company proposed stopping criteria is in line with NICE recommendations for cannabidiol use for the treatment of seizures associated with Dravet Syndrome and Lennox–Gastaut syndrome [16,17].
- The cannabidiol 50 mg/kg/day dose was shown to have a similar level of seizure reduction as 25 mg/kg/day. However, this higher dose was associated with an increased rate of adverse reactions compared to the lower dose. Therefore, the maximum recommended licensed dose is 25 mg/kg/day.
- The GWPCARE6 study was limited to 16 weeks, which is a relatively short period of time considering patients often require lifelong treatment. Preliminary data derived from the extension study suggests the treatment effect observed for cannabidiol during the pivotal study is maintained over time at doses ≤ 25 mg/kg/day. However, a large proportion of patients had discontinued treatment by week 72[1].
- There is a cannabidiol dose-related increase in the incidence of treatment related adverse effects. Clinical experts sought by AWTTC highlight patients would be closely monitored, and treatment would be stopped if adverse events were not manageable.
- The health-related quality of life changes in the patient's overall condition improved and were maintained in the extension study.
- Cannabidiol is an oral solution, which may be beneficial for patients who have swallowing difficulties.
- A large placebo response was observed in the GWPCARE6 study. However, this is commonly seen in epilepsy trials including the cannabidiol clinical trials for Dravet Syndrome and Lennox–Gastaut syndrome[1,16,17].

4.0 COST-EFFECTIVENESS

4.1 Content

The company submission includes a cost-utility analysis (CUA) comparing cannabidiol oral solution (2.5 mg/kg up to a maximum 12.5 mg/kg dose twice daily) as adjunctive treatment of seizures associated with tuberous sclerosis complex (TSC) plus usual care (defined as a combination of AEDs) compared to usual care alone for patients 2 years of age and older[1].

The CUA takes the form of a cohort-level model using regression models to predict the expected probability of seizure-free days and associated seizure frequency, with 1-week cycles, a 100-year lifetime horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at a rate of 3.5% where the time horizon exceeds one year. The submission incorporates a simple Patient Access Scheme discount (PAS). The model comprises three health states: alive and on treatment with cannabidiol plus usual-care, alive and on treatment with usual-care only and death. Patients enter the model in either one of the 'Alive' states. Patients in the 'Alive and on treatment with cannabidiol plus usual-care' health state move to the 'Alive and on treatment with usual-care only' health state if they discontinue treatment. For both 'Alive' health states, a binomial regression model predicts the proportion of seizure-free days per 7-day cycle based on trial efficacy data for the cannabidiol 25 mg/kg/day arm from the GWPCARE6 trial[14]. A fitted negative binomial model then predicts the total seizure frequency on the non-seizure-free days per cycle to allow distribution of the cohort in different seizure frequency categories. Different seizure frequency categories were defined for resource use purposes and health-related quality of life (HRQoL). Resource use categories were defined to accurately capture the clinician experience of resource use associated with different frequencies of seizures (including no seizures per week, ≤ 2 seizures per week, > 2 and ≤ 7 seizures per week, and > 7 seizures per week). HRQoL categories were defined to appropriately capture the impact of seizures on patient and caregiver quality of life and were based on the number of seizures per day. The model uses these predicted distributions to calculate the proportions of the cohort that is assigned to each seizure frequency health state within the 'Alive' health states. Once patients are assigned into sub-health states based on seizure frequency, they are split between generalised seizures and focal with impairment of awareness seizures for each state based on 16-week data of the GWPCARE6 trial to calculate healthcare resource use and health-related quality of life per cycle[14]. Furthermore, the trial population was divided into four age groups (2-6 years, 7-11 years, 12-17 years and 18-65 years) based on GWPCARE6 patient-level data to allow a more precise estimation of the weight-based treatment dosages of cannabidiol and account for the difference in healthcare resource use between paediatric patients and adults identified in a Delphi panel study[14,18].

The model includes all serious treatment-emergent adverse events classified as severe and considered to be treatment-related (e.g. vomiting, nausea, fatigue, liver injury, hypersensitivity etc.) which occurred during the 16-week GWPCARE6 treatment period[14]. Discontinuation due to adverse events was applied based on 16-week and 52-week follow-up data (for the cannabidiol arm) of the pivotal trial and were applied equally across all health states, regardless of seizure frequency[14,15]. Longer-term discontinuation rates beyond 68 weeks were based on NICE health technology appraisal guidance for the use of cannabidiol in Dravet syndrome[16]. Cannabidiol treatment is assumed to be stopped if the seizure frequency has not decreased by at least 30% from baseline or over the last 6 months based on the cannabidiol indications approved by NICE for Dravet Syndrome (DS) and Lennox–Gastaut syndrome (LGS) with the proportion of patients who stop treatment at 6 and 12 months based on the treatment period in the extension study with 18 and 24 months assumed to be the

same as at 12 months[15-17]. All patients who discontinue or stop treatment will move to the 'Alive and on treatment with usual-care only' health state. Mortality included in the model comprised of general mortality, based on Office for National Statistics life tables for Wales[19] excess TSC mortality and sudden unexpected death in epilepsy[20,21]. A reduced effect of TSC-associated neuropsychiatric disorders (TAND) on healthcare resource use and quality of life based on published evidence and expert opinion was applied to patients aged 2 to 6 years who experienced a reduction of seizure frequency of at least 50% following treatment initiation[1,22].

A weighted average cost of all available AEDs (obtained from published sources[23,24]) was used to calculate the per-cycle usual care cost based on prescription share and the age group distribution from the GWPCARE6 clinical trial[14,25]. A liver function test and liver monitoring for cannabidiol in addition to the routine monitoring for patients receiving AEDs were included in the model[26]. Healthcare resource use based on age (paediatric and adult), seizure frequency per week and seizure type was estimated through a two-round Delphi panel study and costed using published unit costs[18,27]. Cost of adverse events was based on data from the pivotal trial regarding severity of adverse events and requirement for hospitalisation. Subsequent treatment upon discontinuation was assumed to include everolimus for 7.6% of patients[28]. Furthermore, TAND costs were based on published values[29].

The models account for patient quality of life and assigns utility decrements for caregivers based on seizure frequency and type. Since utility data were not collected as part of the pivotal trial and no suitable evidence was identified in the literature, the company conducted a vignette study of 200 members of the general population using time trade off methodology to elicit utility weights for patients and caregivers which were then interpolated for seizure type and frequency combinations for the TSC-associated epilepsy health states[1,14,30]. A disutility based on a Dutch published vignette study was applied for adverse events[31]. Moreover, utility increments were applied where TANDs were considered to be reduced based on published values[32-35].

Extensive deterministic and probabilistic sensitivity analyses and scenario analyses were conducted to test the influence of the uncertainty of individual parameters on the model results.

4.2 Results

The results of the base case are detailed in Table 3. When compared with usual care alone, add-on cannabidiol is [commercial in confidence figures removed] more costly and produces an additional [commercial in confidence figures removed] quality-adjusted life-years (QALYs) over the lifetime horizon. The higher cost for cannabidiol is predominantly driven by the higher acquisition costs though this is partially offset by lower healthcare costs.

Table 3. Results of the base case analysis

	Cannabidiol + usual care	Usual care only	Difference
Medicine acquisition costs	¶¶	£21,777	¶¶
Administration costs	£0	£0	£0
Healthcare costs (including primary and secondary care, monitoring and adverse events)	¶¶	£919,479	¶¶
Total costs	¶¶	£941,256	¶¶
Total QALYs	¶¶	-4.58*	¶¶
ICER (£/QALY gained)	¶¶		

[commercial in confidence figures removed]
¶¶: commercial in confidence figure removed
*Negative QALYs are caused by the inclusion of carer utilities as decrements.
ICER: incremental cost-effectiveness ratio; Usual care: combination of different AEDs; QALY: quality-adjusted life-year

In deterministic sensitivity analysis, the ICERs for cannabidiol plus usual care compared to usual care alone ranged from [commercial in confidence figures removed]. The stopping rule assessment rate applied at 6 months for patients with a seizure frequency greater than seven seizures per week, the highest seizure frequency category, followed by the number of caregivers, the patient utility values applied to seizure-free patients, and response rates used to estimate the proportion of patients who benefit from a reduction in TAND symptoms impacted most on cost-effectiveness results. The results of the scenario analyses are assessed in order of plausibility in Table 4.

Probabilistic sensitivity analyses indicate that cannabidiol plus usual care has 85% and 98.3% probability of being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

Table 4. Results of scenario analyses

Scenarios	ICER	Plausibility
Caregiver disutility and TAND costs and utilities excluded	¶¶	While the inclusion of caregiver quality of life and wider costs and benefits as presented in the base case analysis can be taken into consideration under the AWMSG appraisal process for a medicine for a rare disease[36], it confuses the perspective of the analysis.
Carer disutility excluded	¶¶	This scenario is plausible as, while the inclusion of caregiver quality of life and wider costs and benefits as presented in the base case analysis can be taken into consideration under the AWMSG appraisal process for a medicine for a rare disease[36], it confuses the perspective of the analysis.
TAND costs and utilities excluded	¶¶	This scenario is plausible as it is uncertain whether these wider costs and benefits would be achieved in routine practice.
Varying discount rate between 0% and 6%	¶¶	This scenario is plausible as it is based on standard ranges used for sensitivity analysis.
Patient utility taken from Tritton et al. 2019[37]	¶¶	This scenario is plausible as it is based on published evidence.
Patient utility taken from Vergeer et al. 2019[38]	¶¶	This scenario is plausible as it is based on published evidence.

Scenarios	ICER	Plausibility
Social care and educational costs included	**Cannabidiol dominates**	This scenario is plausible as social care and educational costs will arise. However, this wider perspective includes costs other than those relevant to the NHS and Personal Social Services
Using a dose of 25mg/kg/day for all patients	¶¶	While this scenario is less plausible as in routine practice not all patients would receive maximum dose, it reflects the population of the pivotal trial on which all clinical outcomes are based in the model[14].
Both treatment arms lose the placebo response observed in the GWPCARE6 trial at 6 months following the trial end	¶¶	The plausibility of this scenario is uncertain. While the results of the two-round Delphi panel study suggest that placebo response may subside after 6 months, there is no evidence to corroborate this assumption[18].
No adjustment made for placebo response in either treatment arm	¶¶	The plausibility of this scenario is uncertain. While the results of the two-round Delphi panel study suggest that placebo response may subside after 6 months, there is no evidence to corroborate this assumption[18].
10% reduced cost for AEDs in cannabidiol arm	¶¶	The plausibility of this scenario is uncertain. While data from the US expanded access programme for LGS and DS showed that 52% of patients taking valproate reduced their dose while taking cannabidiol, no such evidence exists for TSC[39].
Average cannabidiol dose reduced to 10mg/kg/day	¶¶	The plausibility of this scenario is uncertain. While the cannabidiol Summary of Product Characteristics for TSC-associated seizures states a target dose of 10mg/kg/day, it is unlikely that all patients will remain on this low dose[10].
Lowest base case utility associated with TAND symptoms[32]	¶¶	The plausibility of this scenario is uncertain as it is unclear upon what evidence the change was based.
TAND benefit applies to all patients	¶¶	This scenario is less plausible as the company's Delphi panel consensus suggests that TAND would only have benefit if seizures can be reduced early in childhood[18].
TAND benefit applied for 5 years only	¶¶	This scenario is less plausible as the company's Delphi panel consensus suggests that TAND benefit is likely to last[18].
30-year time horizon	¶¶	This scenario is less plausible since TSC-associated epilepsy is a long-term condition that affects children and young adults and 30 years may not capture all costs and outcomes accrued.
Subsequent treatment (with everolimus) not included	¶¶	This scenario is less plausible considering that everolimus is part of treatment of a small number of patients.
3 caregivers assumed (to reflect impact on wider family)	¶¶	This scenario is less plausible as, while it is likely that there are several caregivers per patient, it cannot be assumed that every patient has 3 caregivers.

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed and transparent account of the methods and data sources used in the analysis.
- The model is well presented and appears robust and well-structured.
- Reasonable justifications are provided for the assumptions applied in the model.
- The company has aimed to use the best available data.

Limitations:

- The model accounts for reductions in quality of life of two caregivers per patient. While the company states that inclusion of caregiver quality of life has been considered in SMC and NICE appraisals for cannabidiol in DS and LGS[16,17], and other HTA submissions due to the high impact these diseases have on daily life for caregivers, the inclusion confuses the perspective of the cost-utility analysis and increases cost-effectiveness. Furthermore, no caregiver costs are included which will skew the cost-effectiveness results. Removing caregiver utilities from the model results in an ICER of [commercial in confidence figures removed].
- The treatment effect of cannabidiol was assumed to be sustained in the long-term at the level observed during the 16-week trial period. While this is corroborated by the open-label extension study results which show sustained effect over 72 weeks, any change in effectiveness over time will impact the cost-effectiveness of cannabidiol[15]. However, the company states that this assumption may be conservative considering the observed longer-term data shows fewer patients remaining in the higher seizure frequency health states and more patients entering the seizure-free health state over time[15].
- AWTTC-sought clinical expert opinion suggests an average cannabidiol dose of 12 mg/kg/day for the indication under consideration and the model uses this as an average dose. However, the efficacy data is based on the dose of 25 mg/kg/day which was used in the GWPCARE6 trial[14]. It cannot be assumed that the efficacy outcomes in the GWPCARE6 trial will be observed at the lower 12 mg/kg/day modelled dose and that therefore the company base case ICER estimate is representative of what would be expected in practice. Given that the maximum dose of cannabidiol is 25 mg/kg/day, this could underestimate the cost of cannabidiol treatment if higher doses were to be used more frequently in routine practice.
- A large placebo effect was observed in the control group with reductions of seizure frequency of 27% over the entire study period of 16 weeks compared to 49% in the cannabidiol group. This placebo effect was considerably higher than the expected effect of 15%[1,2,14]. Based on expert opinion and a published review of evidence stating that this placebo effect was likely to cease after 6 months, control patients were reverted back to baseline seizure frequency after 6 months in the model[40]. This could overestimate the effectiveness and cost-effectiveness of cannabidiol were the placebo effect to continue beyond 6 months.
- TSC-associated seizures are a complex condition with varying treatment options that also depend on the age of the patient. While the company undertook a two-round Delphi panel study including 10 clinical experts from the UK to provide estimates for the model parameters for which no data were available from the GWPCARE6 clinical trial or published literature (e.g. for annual healthcare resource use, the effects of TAND on healthcare resource

use and quality of life or changes of healthcare resource use with age), the average estimation may not accurately reflect the variability and complexity in routine practice[14,18]. While this appears to be the best available data at this point, the use of estimates based on clinical opinion will introduce bias.

- In the absence of data from the pivotal trial and published literature, utilities used in the model were elicited through a vignette study of 200 members of the general public using time trade off[30]. While the vignette study seems to have been robustly conducted, the lack of prospective utility data will introduce bias of unknown magnitude.
- It is unclear whether the modelled population, based on GWPCARE6 patients that had failed a median of 4 AEDs prior to entering the trial reflects the place in therapy that will be observed in practice i.e. cannabidiol use once two other appropriate AEDs, trialled to a maximally tolerated dose, that have failed to achieve seizure control.
- The pivotal trial included patients aged 1 years old. However, the licensed indication is for use from 2 years onwards. Inclusion of younger children in the trial could introduce bias of unknown proportion[14].
- Clinical efficacy of cannabidiol (i.e. seizure-free days and seizure frequency) was taken from the 16-week follow-up period of the pivotal trial based on the entire study population (no division by age)[14]. Considering that most other input parameters are split into age groups, this could introduce bias. However, the company states that no significant differences in treatment effect based on age were found.
- No longer-term discontinuation data beyond 68 weeks was available from the pivotal trial and extension study [14,15]. Therefore, long-term discontinuation rates were taken from the NICE cannabidiol submission for LGS[17], as discontinuation rates were assumed to follow a similar trajectory in TSC-associated epilepsy. Any differences in long-term discontinuation rates will introduce bias.
- The proportion of patients who would be expected to stop treatment at 18 months and at 24 months is assumed to be the same as at 12 months, as the available extension study data were limited to 12 months[15]. Furthermore, baseline patient seizure frequency used to inform the stopping rules was only measured in the 28 days before treatment start but assumed to represent the '6 months before starting treatment' period. This may cause bias and uncertainty regarding discontinuation rates.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) did not identify any studies relevant to the cost-effectiveness of cannabidiol oral solution as adjunctive treatment of seizures associated with TSC compared to usual care (defined as a combination of AEDs) for patients 2 years of age and older.

5.0 BUDGET IMPACT

5.1 Context and methods

The company estimates that 67 patients currently have treatment-refractory TSC-associated epilepsy in Wales. This is based on a prevalence of TSC in Europe of 1 in 18,861 which was estimated as the average of published values from the UK, Northern Ireland and Sweden and a proportion of TSC patients suffering from epilepsy of 80% of which 62.5% will be refractory to current treatment[41-46], extrapolated to the Welsh population between 2 and 65 years[47]. This prevalence is assumed to rise to 70 patients by Year 5, accounting for population growth[48]. Annual new incidence is assumed to be 0 in Year 1 and 1 in subsequent years, based on an incidence of TSC

of 1 in 10,140 live births and Welsh birth statistics[49,50], adjusted and extrapolated as above. Taking into account mortality, a total number of 67 patients are assumed to be on treatment in Year 1, increasing to 69 in year 5, all of which are considered eligible for treatment with cannabidiol. The company estimates an uptake rate of [commercial in confidence figures removed] in Year 1, increasing to [commercial in confidence figures removed] in Year 5 and adjusts for discontinuation and stopping of treatment[14]. Annual costs of [commercial in confidence figures removed] in Year 1, increasing to [commercial in confidence figures removed] in Year 5 (based on children growing and gaining weight over time) were applied for cannabidiol and £1,107 to £1,178 for usual care, respectively. AED cost is assumed to be reduced by 10% for patients receiving cannabidiol.

The company provided basic sensitivity analysis, altering uptake rate by +/-5%.

5.2 Results

The budget impact is presented in Table 5. The company estimates that introducing cannabidiol oral solution would lead to an overall cost of [commercial in confidence figures removed] in Year 1, increasing to [commercial in confidence figures removed] in Year 5 with an overall budget impact over the 5-year period of [commercial in confidence figures removed]. This estimate incorporates cost differences resulting from the displacement of usual care. Basic sensitivity analysis undertaken by the company suggests budget impact to be in the range from [commercial in confidence figures removed] over the 5-year time horizon.

Table 5. Company-reported costs associated with use of cannabidiol oral solution as adjunctive treatment of seizures associated with tuberous sclerosis complex (TSC) compared to usual care (defined as a combination of AEDs) for patients 2 years of age and older.

	2021	2022	2023	2024	2025
Sub-population of eligible patients (indication under consideration)	67	68	68	69	69
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine allowing for discontinuations	¶¶	¶¶	¶¶	¶¶	¶¶
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	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶: commercial in confidence figure removed

The company estimates that net resource implications arising from the introduction of cannabidiol will lead to a saving of [commercial in confidence figures removed] in Year 1, increasing to [commercial in confidence figures removed] in Year 5. This is mainly a consequence of savings in secondary and tertiary care costs. These resource type savings are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The submission gives a transparent account of the methods and data sources used to estimate budget impact. The company has also factored increased weight of patients as children grow, discontinuation, population growth and mortality into the calculations.
- The budget impact presented assumes patients receiving cannabidiol will have a reduced use of AEDs. However, considering that cannabidiol is to be used in addition to usual care, this would lead to an underestimation of the budget impact if these reductions were not realised in routine practice.
- The references used for estimate the prevalence of TSC-associated epilepsy are dated[41-43], and any changes in prevalence in the last 20 years are not taken into account.
- It is unclear whether the costs used for the model include costs associated with TAND.

6.0 ADDITIONAL FACTORS TO CONSIDER

6.1 Medicines developed to treat rare diseases

The applicant company suggests cannabidiol should be considered as an orphan medicine.

AWTTC considers cannabidiol eligible to be appraised as an orphan medicine. The medicine has EMA designated orphan status. The full licensed indication for cannabidiol includes the use for epilepsy associated with Dravet syndrome, Lennox-Gastaut syndrome and tuberous sclerosis complex. Welsh clinical expert opinion indicates the full population of the licensed indication does not exceed the threshold of ≤ 5 patients in 10,000 (≤ 1,500 patients in Wales).

New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 6) if they consider cannabidiol is a medicine developed to treat a rare disease and the cost per QALY is above the normal thresholds applied.

Table 6. 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 tumours which can form throughout the body. 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, with seizures occurring in up to 90% of patients[4]. These often start as infantile spasms and develop into focal (or partial) seizures, however other seizure types such as tonic-clonic, atonic and myoclonic have been reported[51]. Patients with TSC-associated epilepsy may develop significant comorbidities, such as autism spectrum disorders and cognitive impairment/delay which may cause long-term detrimental effects[52,53].
Unmet need	There is a significant unmet need due to inadequate seizure control in TSC-associated epilepsy. Current practice is 'usual care' which is use of either single or combination AEDs although everolimus may be offered to patients with refractory partial onset seizures and in whom other non-pharmacological interventions, such as epilepsy surgery and/or vagus nerve stimulation (VNS), has failed or is not considered suitable[1]. At least one-third of patients are known to have refractory epilepsy with their seizures not successfully controlled by existing AEDs[2]. Any new therapeutic approaches for the treatment of epilepsy in TSC could be used to improve seizure control, cognitive function, and patient quality of life.
Innovative nature of the medicine	The applicant company claims that cannabidiol represents a step-change in the treatment of TSC-associated epilepsy. Cannabidiol has been shown to be clinically effective and offers a unique therapeutic modality with a favourable safety and tolerability profile in patients with TSC-associated epilepsy who live with the constant threat of seizures and who otherwise have extremely limited treatment options[14].
Societal impact on non-health benefits that may not adequately be captured in the QALY	The company suggests that cannabidiol is likely to improve the quality of life of the wider family, including siblings and increase caregiver productivity and the associated societal benefits of the parent(s)/primary caregiver(s) not giving up work to care for a patient with TSC-associated epilepsy. A period of seizure-free time may give patients the opportunity to learn, play and develop new skills, allow families to undertake 'everyday' activities previously considered unthinkable, such as playing outside, visiting relatives or going on holiday and make parents/caregivers feel less anxious about the potential for injury or death of the child with TSC-associated epilepsy and able to focus on their own lives and on the child's siblings. Furthermore, patients may be able to live at home with family rather than needing to be cared for in a specialist institution, which reduces the burden on society. Cannabidiol has the potential to decrease the number and frequency of seizures enabling a better quality of life for patients and their families.
Does the medicine cure or reverse rather than stabilise the condition?	Cannabidiol does not reverse or cure the condition.
Does the medicine bridge a gap to a definitive therapy?	Cannabidiol does not bridge a gap to a definitive therapy. Cannabidiol 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

Primary endpoint of the GWPCARE6 study

The primary endpoint of the GWPCARE6 study was the change from baseline in number of TSC-associated seizures for cannabidiol compared to placebo during the treatment period. TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures[2].

Subject or caregiver global impression (S/CGIC) scores

Subject/Caregiver Global Impression of Change (S/CGIC) score is a self-report measure using a 7-point subject or caregiver rated scale ranging from 1 (very much improved) to 7 (very much worse). Change is defined as a score of 1 (very much improved), 2 (much improved), 3 (a little improved), 4 (no change), 5 (a little worse), 6 (much worse) or 7 (very much worse) on the scale[1].

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