Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2402

cannabidiol 100mg/mL oral solution (Epidyolex®)

GW Pharma Ltd

14 January 2022

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

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

cannabidiol (Epidyolex®) is accepted for use within NHSScotland.

Indication under review: for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older.

Cannabidiol reduced TSC-associated seizure frequency compared with placebo in one randomised, double-blind, phase III study in patients with TSC-associated epilepsy that was inadequately controlled by other anti-epileptic drugs.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

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

Chairman
Scottish Medicines Consortium

Indication

For use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older.[1]

Dosing Information

The recommended starting dose of cannabidiol is 2.5mg/kg taken twice daily (5mg/kg/day) for one week. After one week, the dose should be increased to a dose of 5mg/kg twice daily (10mg/kg/day) and the clinical response and tolerability should be assessed. Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5mg/kg administered twice daily (5mg/kg/day) up to a maximum recommended dose of 12.5mg/kg twice daily (25mg/kg/day).

Any dose increases above 10mg/kg/day, up to the maximum recommended dose of 25mg/kg/day, should be made considering individual benefit and risk and with adherence to the full monitoring schedule.

Cannabidiol should be initiated and supervised by physicians with experience in the treatment of epilepsy.[1]

Product availability date

April 2021

Cannabidiol (Epidyolex®) meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Tuberous sclerosis complex (TSC) is a rare, chronic, genetic disorder caused by a mutation in the TSC1 gene or TSC2 gene which is characterised by the development of benign tumours (or tubers) in multiple organs. These mainly occur in the brain, eyes, heart, kidney, skin and lungs and result in the most common clinical presentations of epilepsy, autism and cognitive impairment and neonatal cardiac rhabdomyomas. Cannabidiol has received marketing authorisation for use as adjunctive therapy of seizures associated with TSC for patients 2 years of age and older. Cannabidiol (Epidyolex®) has previously been accepted for use in NHSScotland as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, for patients 2 years of age and older (SMC2262 and SMC2263).[1, 2]

The evidence to support the use of cannabidiol for TSC-associated seizures comes from one randomised, double-blind, phase III study (GWPCARE6). The study comprised a 4-week baseline period and a 16-week treatment period (including a 4-week titration period and 12-week maintenance period). Eligible patients were aged 1 to 65 years with a clinical diagnosis of TSC (by 2012 International Tuberous Sclerosis Complex Consensus Conference) and had been taking at least one anti-epileptic drug at a stable dose for ≥4 weeks. They had at least eight TSC-associated seizures during the 4-week baseline period, with at least one seizure occurring in at least 3 of the last 4 weeks. Eligible patients were randomised equally to receive cannabidiol 25mg/kg/day

(n=75), cannabidiol 50mg/kg/day (n=73) or matching placebo (n=76). Study medication was taken orally daily in two equally divided doses. In both active groups, cannabidiol was initiated at a dose of 5mg/kg/day and titrated in increments of 5mg/kg/day every 2 days until day 9 when 25mg/kg/day was reached. Patients in the 25mg/kg/day group continued on this dose to week 16. Patients in the 50mg/kg/day group continued to titrate in increments of 2.5mg/kg/day every 2 days until day 29 when 50mg/kg/day was reached and continued on this dose to week 16. Patients were to remain on the target dose for the duration of the treatment period but investigators could reduce the dose or suspend or amend titration if unacceptable toxicity occurred. Randomisation was stratified according to age groups (1 to 6 years, 7 to 11 years, 12 to 17 years and 18 to 65 years). All study patients received current clinical management which included any concomitant anti-epileptic medicines and any non-pharmacological treatment (for example ketogenic diet, vagus nerve stimulation) which had been stable for ≥4 weeks before screening and remained so during the study period. Rescue medication was allowed when necessary and was recorded. Patients who completed the double-blind phase could enter an open-label extension study.[2, 3]

The primary outcome was the change from baseline in the number of TSC-associated seizures during the 16-week treatment period assessed in the intention-to-treat (ITT) population, which included all randomised patients with post-baseline efficacy data. TSC-associated seizures were defined and agreed by the European Medicines Agency (EMA) and the Epilepsy Study Consortium independent committee of experts as countable 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 generalised convulsive seizures (Type 3 focal) and generalised tonic-clonic, tonic, clonic or atonic seizures. Patients or caregivers completed a daily patient diary to record the number, type and severity of seizures.[2, 3] A hierarchical statistical testing strategy was applied to test the primary and key secondary outcomes between both cannabidiol groups and placebo. The key secondary outcomes were TSC-associated seizure treatment responders (defined as ≥50% reduction in TSC-associated seizure frequency), patient or caregiver's Global Impression of Change (CGIC) and the change in total seizures.

There was a statistically significant reduction in TSC-associated seizures in the cannabidiol 25mg/kg/day group compared with placebo. However, since the first key secondary outcome (TSC-associated seizure treatment responders between cannabidiol 25mg/kg/day and placebo) failed to reach statistical significance (p=0.069), further formal statistical testing was not performed and the results reported for the subsequent outcomes are descriptive only and non-inferential (no p-values reported). The cannabidiol 50mg/kg/day group had similar efficacy results to the 25mg/kg/day group but due to a higher adverse event rate, only the 25mg/kg/day dose received marketing authorisation. Therefore, results are presented for the cannabidiol 25mg/kg/day and placebo groups only. Details are presented in table 1.

Table 1: Results for the primary and key secondary outcomes of the GWPCARE6 study

	Cannabidiol 25mg/kg/day (n=75)	Placebo (n=76)
TSC-associated seizures during 28-day baseline period	56.0	54.1
Percentage change in TSC-associated seizures during the treatment period	49%	27%
Percentage reduction versus placebo (95% CI)	30% (14% to 43%) p=0.0009	
Patients with ≥50% reduction in TSC-associated seizures from baseline	36% (27/75)	22% (17/76)
Odds ratio versus placebo (95% CI), p-value	1.95 (0.95 to 4.00) p=0.069	
Patient or caregiver global impression of change score as improved	69% (48/70)	39% (30/76)
Odds ratio versus placebo (95% CI)	2.25 (1.24 to 4.07)	
Total seizure frequency (in 28 days) at baseline, median	56.0	56.5
Total seizure frequency (in 28 days) during treatment period, median	32.96	44.03
Change in total seizures	48%	27%
Treatment ratio (95% CI)	0.71 (0.58 to 0.87)	

TSC=tuberous sclerosis complex; CI=confidence interval

Additional secondary outcomes favoured cannabidiol over placebo. These included the percentage of patients with ≥75% and 100% reduction in TSC-associated seizures from baseline which was achieved by 16% versus 0% and 1.3% versus 0% in the cannabidiol 25mg/kg/day and placebo groups respectively; change from baseline in TSC-associated seizure-free days reported as LS mean per 28 days was 6.23 versus 3.41 respectively.

Health Related Quality of Life (HRQoL) was assessed using Quality of Life in Childhood Epilepsy (QOLCE) for patients aged 2 to 18 years and the Quality of Life in Epilepsy (QOLIE) for patients aged ≥19 years. For both tools, the overall score ranges from 0 to 100 with, higher scores indicating better quality of life. In younger patients, there was a LS mean change from baseline in QOLCE of 2.9 in the cannabidiol 25mg/kg/day group (n=35) versus 2.4 in the placebo group (n=38); difference 0.5 (95% CI: -4.7 to 5.6). In adult patients, there was a LS mean change from baseline in QOLIE of -1.2 in the cannabidiol 25mg/kg/day group (n=10) versus 1.7 in the placebo group (n=10); difference -2.9 (95% CI: -16.8 to 10.9).[2, 4]

Patients who completed GWPCARE6 could enter an open-label extension study including an initial 2-week blinded transition to cannabidiol 25mg/kg/day and a 3-week titration period to optimise the dose up to a maximum of 50mg/kg/day (which is higher than the recommended dose) for a maintenance period of up to 2 years. The extension study primarily assessed safety but there were

a number of secondary outcomes on efficacy. Available results from the open-label extension are after a median treatment time of 267 days (range 18 to 910) and the mean modal dose was 27mg/kg/day. Interim analysis after 48 weeks found that, when measured in 12-week windows over 48 weeks, the median reductions in seizure frequency were 54% to 68%. A ≥50% reduction in seizure frequency was achieved by 53% to 61% of patients and 6% to 11% were seizure-free.[5, 6]

Summary of evidence on comparative safety

In the GWPCARE6 study at the end of the 16-week treatment period, a treatment-emergent adverse event was reported by 93% (70/75) of cannabidiol 25mg/kg/day patients and 95% (72/76) of placebo patients and these were considered treatment-related in 69% and 52% respectively. In the cannabidiol 25mg/kg/day and placebo groups respectively, patients with a reported serious adverse event were 21% versus 2.6%, and patients discontinuing therapy due to an adverse event was 11% versus 2.6%.[2, 3]

The most frequently reported treatment-emergent adverse events of any grade in the cannabidiol 25mg/kg/day versus placebo groups respectively were: diarrhoea (31% versus 25%), decreased appetite (20% versus 12%), pyrexia (19% versus 7.9%), vomiting (17% versus 9.2%), increased gamma glutamyl transferase (16% versus 0%), nasopharyngitis (15% versus 16%), somnolence (13% versus 9.2%), increased alanine aminotransferase (12% versus 0%), increased aspartate aminotransferase (11% versus 0%), constipation (11% versus 7.9%), cough (11% versus 6.6%), upper respiratory tract infection (9.3% versus 13%). Increased levels of liver enzymes were the most frequently reported serious adverse events.

The number of concomitant anti-epileptic medicines taken by a patient affected the safety profile of cannabidiol; patients receiving more than four concomitant anti-epileptic medicines had a higher incidence of serious treatment-emergent adverse events and adverse events leading to discontinuation, as well as with somnolence-related adverse events. In addition, adverse events of somnolence, rash and pneumonia were reported in more patients taking cannabidiol 25mg/kg/day with clobazam compared to cannabidiol alone.[2, 3]

The summary of product characteristics notes that each mL of cannabidiol oral solution contains 79mg of ethanol. This is equivalent to 10% v/v anhydrous ethanol, that is up to 691.3mg ethanol/ per maximal single cannabidiol dose (12.5mg/kg) for an adult weighing 70kg (9.9mg ethanol/kg). For an adult weighing 70kg, this is equivalent to 17mL of beer, or 7mL of wine per dose.[1]

Summary of clinical effectiveness issues

Tuberous sclerosis complex (TSC) is a rare, chronic, genetic disorder and epileptic seizures are the most common neurological feature affecting 90% of patients over a lifetime. Many patients experience multiple seizure types, often focal, and although infantile spasms are often the first and may resolve over time, the frequency and severity of other seizures often increase throughout early childhood and may persist into adulthood. The aim of treatment is to prevent or control seizures which may improve cognitive neurodevelopment and quality of life. Patients with seizures

associated with TSC are treated with combinations of anti-epileptic medicines with choice dependent on seizure type, patient's age and safety profile of the medicine (including vigabatrin, lamotrigine, levetiracetam, carbamazepine, felbamate, valproate and clobazam) as well as steroids or corticotropin. Nearly two-thirds of patients develop medically intractable epilepsy and sudden unexpected death in epilepsy is one of the most common causes of death. Patients may also receive non-pharmacological management.[2, 7] A dispersible tablet formulation of everolimus is the only other medicine licensed for adjunctive treatment of TSC-associated seizures and is specifically for patients aged 2 years and older with refractory partial onset seizures, with or without secondary generalisation.[8] Everolimus has been accepted for use in NHSScotland. The company suggests that everolimus is considered a last-line treatment and that cannabidiol would be used before it. However, clinical experts consulted by SMC had mixed views and indicated that everolimus may be used earlier in the treatment of focal seizures in some patients. Cannabidiol meets SMC orphan criteria for this indication.

The evidence from GWPCARE6 demonstrated a significant reduction in the primary outcome of TSC-associated seizure frequency in patients treated with cannabidiol (25mg/kg/day) compared with placebo. Although the first key secondary outcome (patients with ≥50% reduction in TSC-associated seizures) did not reach statistical significance, the difference between cannabidiol and placebo was considered supportive by the EMA. The treatment effect was considered to be clinically relevant.[2, 3]

Controlled treatment was limited to 16 weeks (4-week titration and 12-week maintenance), although there is longer term data available in patients with severe epilepsies. The treatment effect of cannabidiol on longer term outcomes including neurodevelopment problems, learning disabilities, status epilepticus and sudden death are not available. In addition, the longer term adverse effects of cannabidiol on children is unknown. The ethanol content of the oral solution should also be considered for children and high-risk patients.

The cannabidiol dose used in GWPCARE6 is high compared with the recommended dose. In GWPCARE6, patients were randomised to the maximum (25mg/kg/day) or double the maximum recommended dose (50mg/kg/day) regardless of clinical response. Dose titration was also much faster (every 2 days compared with every week). There is a lack of evidence for patients with TSC-associated seizures who received a dose of 10mg/kg/day, however, the treatment effect of the 25mg/kg/day and 50mg/kg/day groups in GWPCARE6 were similar and do not provide an indication of dose-response relationship. There is some evidence of efficacy for cannabidiol 10mg/kg/day from the GWPCARE2 study in patients with Dravet syndrome and the GWPCARE3 study in patients with Lennox-Gastaut syndrome but many patients received cannabidiol in combination with clobazam for these conditions.[1, 2]

The treatment effect on the primary outcome was generally consistent across subgroups but was higher in patients also taking clobazam. Due to the pharmacokinetic interaction between clobazam and cannabidiol, it would have been preferable to stratify randomisation by clobazam use but this was not fully understood at the start of the study. However, pre-specified subgroup analyses found the reduction in TSC-associated seizures was 61% versus 27% in the cannabidiol 25mg/kg/day (n=17) versus placebo (n=25) groups respectively in the subgroup receiving clobazam (odds ratio 0.53 [95% CI:0.36 to 0.80] or difference 47% [20% to 64%]) compared with

44% (n=58) versus 26% (n=51) respectively (odds ratio 0.75 [95% CI:0.59 to 0.96] or difference 25% [3.7% to 41%]) in the subgroup not receiving clobazam. The treatment effect was considered significant and relevant regardless of concomitant clobazam use. Therefore, the marketing authorisation for cannabidiol for TSC-associated seizures is for adjunctive use but not specifically with clobazam while for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, it is in conjunction with clobazam.[1, 2, 4]

The primary outcome was presented as a relative and not absolute treatment effect. There was no information in the absolute change in seizure frequency. There was a higher placebo effect on TSC-associated seizures than expected with a 26.5% reduction from baseline during the 16-week treatment period compared with a 15% reduction anticipated for the power calculation.[2, 3]

Study patients were heavily treated during GWPCARE6 and concomitantly received a median of three (range 0 to 5) anti-epileptics. At baseline, the most commonly used were valproate (45%), vigabatrin (33%), levetiracetam (29%) and clobazam (27%). There were slight differences between the groups in the proportions of patients taking each anti-epileptic and the various combinations is likely to vary between the study and use in clinical practice which may affect the generalisability of study results. In addition during GWPCARE6, only a small proportion of study patients were receiving non-pharmacological treatments (11% used vagus nerve stimulation and 1.3% a ketogenic diet). Use of these additional measures may be higher in clinical practice.[2, 3]

GWPCARE6 enrolled patients aged 1 to 65 years. However, the marketing authorisation is for patients aged 2 years and older due to limited pharmacokinetic, efficacy and safety data in children <2 years.[2]

Study patients in GWPCARE6 were not allowed to receive concomitant everolimus but 9.4% had previously received everolimus.[2, 3] The place in therapy of cannabidiol with respect to everolimus is not clear and may vary in the individual patient depending on seizure type and contra-indications to treatment.

The introduction of cannabidiol for TSC-associated seizures would offer an additional add-on treatment to anti-epileptic medicines for patients who are inadequately controlled. The maximum recommended dose of cannabidiol for TSC-associated seizures is higher (25mg/kg/day) than for other indications (20mg/kg/day) where it is used in combination with clobazam.[1]

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of cannabidiol, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- TSC is a rare and complex, genetic condition and epilepsy is the most common neurological feature, affecting up to 90% of patients. Severe epilepsy can be life threatening and patients often have severe co-morbidities. Patients require round the clock care and so a diagnosis of TSC affects the whole family both physically and mentally.
- More than half of patients with TSC-associated epilepsy do not respond to standard anti-epileptic medicines and there is an unmet need for effective alternative treatment options. Cannabidiol would provide an additional therapeutic option that may help to improve seizure control and quality of life.
- In patients who respond to cannabidiol, improved seizure control may have a direct impact on their daily living, including ability to participate in family and social activities, to go to school and to sleep, all of which may substantially improve their well-being and quality of life. Parents also described increased communication, alertness and responsiveness in their children. Parents of children who have fewer seizures on cannabidiol described the improvements as “life-changing”.
- Improved seizure control may reduce the complications associated with uncontrolled epilepsy and may reduce the risk of hospitalisation, rescue interventions ad sudden unexpected death in epilepsy (SUDEP).
- Any improvements in seizure control can have a substantial impact on relieving the anxiety, stress and pressure on families of caring for a child with TSC. This may allow family and carers time to sleep better, relax and enjoy time with sibling and the wider family. It may allow them the opportunity to enjoy some social activities with their child, improving the well-being and quality of life of family and carers.

Additional Patient and Carer Involvement

We received a patient group submission from the Tuberous Sclerosis Association, which is a registered charity. The Tuberous Sclerosis Association has received approximately 1% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from the Tuberous Sclerosis Association participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost utility analysis comparing cannabidiol and usual care against usual care alone, for the treatment of seizures associated with TSC for patients 2 years of age and older. Usual care consists of a combination of anti-epileptic drugs (AEDs), chosen based on usage across paediatric and adult patients at baseline in the GWPCARE6 study. The company assume that everolimus would be used as a last-line therapy after cannabidiol and therefore excluded it as a comparator in the economic analysis. Ketogenic diet, vagus nerve stimulation and resective surgery are also excluded as they are assumed to be a minimal and established part of the clinical pathway and so would cancel each other out in the incremental analysis.

The analysis uses data from the GWPCARE6 study for treatment effect and is undertaken on the entire patient group 2-65 years and modelled over a lifetime horizon. The perspective of NHS & Personal Social Services Scotland was adopted for costs while patients and 2 caregivers perspective was adopted for outcomes in the original base case. A revised base case reflecting a 'patient only' perspective was provided for consistency with SMC processes but the analysis incorporating carer effects was also considered as a sensitivity analysis.

The economic model is structured as a cohort level regression predicting seizure-free days and seizure frequency using data from the GWPCARE6 study. The model has 3 initial health states: 'alive and on cannabidiol plus usual-care', 'alive and on usual-care' and 'death'. The 'alive' health states are further categorised by seizure frequency on a weekly basis (no seizures, ≤2 per week, >2 ≤7per week, >7 per week) for the purpose of health care resource use, stopping rules and discontinuation. Health states are then further sub-categorized by seizure frequency on a daily basis to calculate HRQoL (seizure- free days, 1 per day, 2 per day, 3-4 per day, ≥5 per day) within each seizure frequency category. The submission proposes the importance of capturing seizure-free days and number of seizures on seizure days separately in TSC. However, in previous epilepsy studies (including previous SMC submissions for similar conditions) a broader approach has been adopted, utilising a Markov model structure and capturing changes in seizure frequency from baseline, i.e. <50% reduction, 50-75% and >75% reduction.

For the purposes of treatment dosages, the trial population is split into four groups: 2-6 years (24%), 7-11 years (25%), 12-17 years (23%), ≥ 18 years (28%). These modelled age groups were aligned to those in GWPCARE6. Baseline age is simulated to increase by 1 year until all patients are aged ≥ 18 years and on adult dosage and services (agreed by a Delphi panel). In the analysis the average cannabidiol dose is 12 mg/kg/day reflecting that, across the cohort of patients, there is a spectrum of doses ranging from < 10 mg/kg/day to the maximum of 25 mg/kg/day.

Treatment effect data were taken from GWPCARE6, over the 16 week study period. While the primary endpoint was reduction in seizure frequency compared to baseline, data for the economic analysis was taken from secondary analyses on (i) seizure frequency and (ii) seizure-free days, both of which showed non-significant trends. The analysis examines the impact of treatment on focal seizures with impairment of awareness and generalized seizures, excluding focal seizures without impairment of awareness, so that resource use and HRQoL associated with each seizure type are included. GWPCARE6 data were used to estimate the proportion of patients who experience

generalized seizures only, focal with impairment of awareness seizures only, or a combination of both seizure types per cycle. The base case uses the week 16 data for the distribution of seizure types which is then assumed to be constant over the model time horizon.

Regression models to predict seizure free-days and frequency by seizure type were explored but could not be found, so instead two mixed effects regression models were run to predict seizure-free days and seizure frequency (on days with seizures), for both seizure types (generalized and focal with impairment of awareness), across two models rather than one. A binomial regression was used to predict seizure-free days per 7-day cycle; then a fitted negative binomial model was used to predict the total seizure frequency on the non-seizure-free days per cycle (aligning with the primary endpoint in GWPCARE6). This allowed for the correlation between seizure frequency and seizure-free days to be captured, as seizure frequency is only estimated for the days in each cycle when patients are expected to have seizures (non-seizure-free days). Random effects were incorporated into the regression analyses. The submission notes that as these regression analyses used a subset of the data for seizures, therefore it is likely to be underpowered to detect statistical difference.

In the long term, the analysis assumes that the predicted seizure frequency and associated seizure-free day distributions at week 16 are maintained for the full model lifetime horizon.

A substantial placebo response was observed in the GWPCARE6 study, as has been observed in previous epilepsy studies. The base case model assumed that this was eliminated in the usual care arm 6 months post trial.

Discontinuation of cannabidiol due to adverse events (AEs) was based on the first 16 cycles/weeks from GWPCARE6 and was applied equally across all health states. After this time, the model applies discontinuation rates based on the open label extension (OLE) study data up to 24 months, with rates varying by seizure category. A longer-term discontinuation rate beyond the OLE was applied for the full lifetime analysis (rate of 0.77%); this is the same value as used in the previous submissions for cannabidiol in Dravet syndrome and Lennox-Gastaut syndrome. A stopping rule was also applied for non-responders - if the seizure frequency has not decreased by at least 30% from baseline at each 6 month interval up to 24 months. In the base case analysis, 7.6% of cannabidiol patients will receive everolimus following treatment discontinuation and in the placebo plus usual-care arm 7.6% will receive everolimus at 2 years after the trial period.

Excess mortality due to TSC is applied equally to both treatment arms and is sourced from published literature. TSC-associated epilepsy causes significant morbidity in the form of TSC-associated neuropsychiatric disorders (TAND). Therefore, the impact of early mitigation of TAND symptoms associated with a reduction in seizure frequency due to treatment with cannabidiol is modelled. There was no evidence from GWPCARE6 so clinical expert opinion in a two- round Delphi panel was sought to derive 6 key areas of impact (intellectual disability, ASD, ADHD, anxiety disorders, and development and behavioural issues) and utility values were derived from various literature reporting costs and utility values for each of these areas.

The health-related quality of life data collected in the GWPCARE6 study (QOLCE and QOLIE) found no significant difference between study arms. Mapping algorithms exist for mapping from QOLIE-31P to EQ5D; however, evidence shows these are not well aligned for mapping.[9] The approach

taken to generating utility values was development of vignettes for patients and carers followed by direct measurement from the UK general population to elicit utility values via a time trade-off (TTO) study. Alternative utility values for patients are identified from the literature and explored in scenario analyses. Carer values are applied as disutilities. The utility values elicited from the vignettes and TTO study for the carers appear to be very low for the multiple seizure per day categories.

All adverse events classified as severe and considered to be treatment-related occurring during the 16-week GWPCARE6 treatment period were included in the analysis. A disutility value for AEs was derived from the literature for epilepsy treatment-related side effects and assumed that this value would be similar across AEs.

The costs in the model include medication (cannabidiol and AEDs), healthcare visits, residential care, subsequent treatment with everolimus, monitoring costs, management of AEs and TAND management. Resource use data was not collected in GWPCARE6 and a systematic literature review identified few papers to inform the analysis, therefore a two-round Delphi panel study was undertaken to elicit the key resource use items.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price.

The base case results with PAS for the preferred base case (patient only perspective) and original company base case (patient and 2 care givers perspective) are shown in table 2

Table 2: Base case results with PAS

	ICER - £/QALY (SMC base case, patient only perspective)	ICER - £/QALY (Company base case, patient and 2 carer perspective)
Cannabidiol + usual care versus usual care alone	22,930	10,074

ICER: incremental cost effectiveness ratio; QALY: Quality adjusted life years

Table 3 presents key sensitivity analyses with PAS for the preferred base case (patient only perspective) and original company base case (patient and 2 care givers perspective).

Table 3: Selected sensitivity and scenario analyses results: with PAS

	Selected scenario analyses – with PAS	SMC base case (patient only) ICER (£/QALY)	Company base case (2 caregivers) ICER (£/QALY)
0	Base case	22,930	10,074
1	Placebo effect maintained both arms	53,166	23,958
1a	Placebo effect lost in both arms at 6 months following the trial end	40,987	18,436
2	Societal perspective (social and educational costs)	Dominant	Dominant
3	Patient utility: Vergeer et al. 2019 (HUI-3)	32,540	11,576

4	Utility values from Verdian et al. 2008	39,961	12,395
5	Requested: Falling treatment effect over time. Provided: discontinuing patients benefit lag 16 cycles	27,431	12, 052
6	Requested: Reduced treatment effect for lower dosage. Provided: Increased cost for dosage 15mg/kg/day Provided: Increased cost for dosage 17.5mg/kg/day	 37,655 49,925	 16,543 21,934
7	Requested: Falling treatment effect & dosage Provided: discontinuing lag & cost 15mg/kg/day Provided: discontinuing lag & cost 17.5mg/kg/day	 43,280 56,487	 19,015 24,818
8	Disutility for only 1 caregiver	13,999	13,999
9	Cost for dosage of 25mg/kg/day	86,735	38,107
10a	Combined 1 & 5 Placebo effect maintained both arm: discontinuing lag & cost 12mg/kg/day	60,313	27,178
10	Requested: combined 1, 5 & 6 Provided: Placebo effect maintained both arm: discontinuing lag & cost 15mg/kg/day Provided: Placebo effect maintained both arm discontinuing lag & cost 17.5mg/kg/day	 85,481 106,455	 38,520 47,971
11	Requested: combined 1, 5, 6 & 8 Provided: Placebo effect maintained both arm: discontinuing lag & cost 15mg/kg/day + 1 caregiver Provided: Placebo effect maintained both arm discontinuing lag & cost 17.5mg/kg/day + 1 caregiver	 53,108 66,138	 N/A N/A

One way sensitivity analyses were undertaken, varying the upper and lower bounds of deterministic values. These included exploring the sensitivity of stopping rules, number of caregivers, utility values applied to seizure-free patients, and response rates estimating the proportion of patients who benefit from a reduction in TAND symptoms. None had a large impact on the ICER. An array of scenario analyses were undertaken, most of which were insensitive on the ICER. The most influential were scenarios regarding the placebo effect. If the placebo effect is not adjusted for, the ICER increase substantially, as shown in table 3, scenario 1.

There were a number of weaknesses associated with the analysis:

- The average dose in economic analysis is 12mg/kg/day, this impacts on costs only, i.e. the treatment effect from GWPCARE6 at 25mg/kg/day is assumed to apply to much lower doses. Additional scenario analyses were requested to explore lower treatment effects for the lower dosage, however, the company maintain there is little evidence of a dosing effect with cannabidiol, so instead they conducted a scenario where the cost of cannabidiol was increased according to higher mean dosages of 15mg/kg/day and 17.5mg/kg/day. This increases the ICER, doubling it from the company base case (table 3 scenario 6). This does not account for any treatment effect uncertainty related to lower doses and there remains a lack of evidence for patients with TSC-associated seizures who receive a dose of 10mg/kg/day. Although there is support for this dosing in patients in LGS and Dravet Syndrome, those patients were also treated with clobazam, which increases cannabidiol levels.

- The base case analysis assumes that the placebo effect is eliminated 6 months post the trial in the usual care arm. No convincing rationale for this was presented. Two previous SMC submissions for cannabidiol (for Dravet syndrome and LGS) do not make this adjustment. SMC clinical experts suggest a placebo effect may persist. If the placebo effect is not adjusted for, the ICER has a substantial increase (table 3 scenario 1, 1a).

- The HRQoL data collected in the GWPCARE6 study (QOLCE and QOLIE) found no significant difference between arms, and the alternative methods described above were used in the economic model to predict substantial gains in QALYs, for both patients and carers, with the carer quality of life aspect comprising more than half of the overall QALY gain for cannabidiol. The impact on carers was acknowledged and while the method used to elicit utility values for this submission is more rigorous than the methods originally used in the previous SMC submissions for cannabidiol in LGS and Dravet Syndrome, there were concerns about the magnitude of the carer quality of life from the inclusion of multiple carers.

- There was a mixed response from clinical experts regarding appropriate comparator. Everolimus could be considered a direct comparator for cannabidiol in a susbset of patients with TSC, or may be given prior to cannabidiol. Ketogenic diet, vagus nerve stimulation and resective surgery could be considered earlier for some TSC patients, so could be offered prior to cannabidiol for some patients, or form part of a relevant comparator treatment. The company were informed of the clinical experts mixed responses, and maintain that cannabidiol would be offered prior to everolimus in the Scottish setting. The place in therapy of cannabidiol is not clear and may vary in the individual patient depending on seizure type and contra-indications to treatment.

- The treatment effect for the economic analysis is taken from the secondary analyses on (i) seizure frequency and (ii) seizure- free days, both of which showed non- significant trends.

- The treatment effect from GWPCARE6 is limited to 16 week follow-up. The analysis assumes that the predicted seizure frequency and associated seizure-free day distribution at week 16 were maintained for the full model lifetime horizon. In reality the effectiveness of cannabidiol could diminish over time, as with other AEDs. A scenario to explore a falling treatment effect over time was requested, but the company maintain there is no clinical evidence to suggest that treatment effect could fall over time so did not undertake the requested analyses. Instead an alternative scenario was undertaken, where patients who discontinue cannabidiol are treated for 16 cycles (weeks) prior to this incurring treatment costs but no benefits. This had a small increasing effect on the ICER (table 3, scenario 5).

- The submission stresses the importance of capturing seizure-free days and number of seizures on seizure days separately in TSC, and is the basis for the approaches taken towards modelling (regression analysis as opposed to a Markov model) and the justification for direct utility value elicitation rather than using previously published values. While it was acknowledged that the regression analysis wasn't in itself an incorrect approach, previous SMC submissions for similar conditions (Dravet syndrome and LGS) used a cohort-level Markov model. A broader approach -as previously taken- may have been able to capture the benefit of reduced seizure frequency yet aligned more closely with existing studies and the evidence base from GWPCARE6.

The Committee considered the benefits of cannabidiol in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as cannabidiol is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted cannabidiol for use in NHSScotland.

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

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN) published guidelines for the diagnosis and management of epilepsy in adults (SIGN 143) in 2015 and updated in 2018 but these do not specifically mention patients with seizures associated with TSC. The SIGN guideline on epilepsy in children has recently been updated and published (SIGN 159, May 2021). This includes a section on tuberous sclerosis and recommends that everolimus could be considered as an adjunctive treatment for children (age 2 years and older) with refractory seizures associated with tuberous sclerosis complex, when other treatments have failed. It notes that children prescribed everolimus should be closely monitored for adverse events.[10, 11]

The National Institute for Health and Care Excellence (NICE) published clinical guideline 137: epilepsies: diagnosis and management in January 2012 and this was updated in May 2021. This does not specifically mention patients with seizures associated with TSC. However, for infants with infantile spasms, this recommends offering vigabatrin as first-line treatment to infants with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid (prednisolone or tetracosactide). Carefully consider the risk–benefit ratio when using vigabatrin or steroids.[12]

UK consensus guidelines for management and surveillance of Tuberous Sclerosis Complex were published in 2019. These guidelines include a section on epilepsy which recommends vigabatrin as first-line therapy for epileptic spasms in infancy with hormonal therapies (oral prednisolone or ACTH) should be used if treatment with vigabatrin is unsuccessful. Anticonvulsant therapy of other seizure types in TSC should generally follow the principles used in other epilepsies. Everolimus should be offered, if possible, to individuals with treatment resistant focal seizures. Epilepsy surgery should be considered for medically refractory TSC patients, but special consideration should be given to children at younger ages experiencing neurological regression. Epilepsy surgery must be performed at designated epilepsy surgery centres in the UK.[13]

The European clinical guidelines developed at the TSC Consensus Meeting for SEGA and Epilepsy Management were published in 2012 and updated in 2018. This provides the following general treatment recommendations for patients with focal seizures:

• First line: vigabatrin for focal seizures before the age of 1 year. Other anti-epileptic medicines that enhance gamma-aminobutyric acid (GABA)ergic inhibition (e.g. topiramate and carbamazepine) after the age of 1 year

• Second line: surgery – usually restricted to those with focal stereotypical seizures and a single EEG focus and is contraindicated in the case of multiple seizure types

• Third line: ketogenic diet, VNS, other anti-epileptic medicines used in focal seizures.[14]

These guidelines predate the availability of cannabidiol for the treatment of seizures associated with TSC.

Additional information: comparators

Current management with antiepileptic medicines, with or without everolimus and non-pharmacological treatments.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Cannabidiol oral solution	5 to 12.5mg/kg orally twice daily	3,714 to 46,426

Costs from MIMS online on 29 September 2021. Costs calculated based on a body weight ranging from 12kg to 60kg. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 19 patients estimated to receive treatment in year 1 and 52 patients in year 5.

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

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

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This assessment is based on data submitted by the applicant company up to and including 17 November 2021.

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

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

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

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

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