Cost-effectiveness of cannabidiol (Epidyolex®) for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome, in conjunction with clobazam, for patients 2 years of age and older.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of cannabidiol (Epidyolex®). Following assessment of the Applicant's submission, the NCPE recommends that cannabidiol (Epidyolex®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (GW Pharmaceuticals) economic dossier on the cost effectiveness of cannabidiol (Epidyolex®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **March 2021**

Summary

In July 2020, GW Pharmaceuticals submitted a dossier of clinical, safety and economic evidence to support the reimbursement application for cannabidiol (Epidyolex®) for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome, in conjunction with clobazam, for patients 2 years of age and older. GW Pharmaceuticals are seeking reimbursement on the High Tech Drug Arrangement. Final data was submitted by the Applicant in December 2020.

Lennox-Gastaut syndrome is a rare, intractable form of severe epilepsy. Drop seizures occur in more than half of patients and usually result from tonic or atonic seizures, which can cause the person to fall suddenly to the ground. Many patients with Lennox-Gastaut syndrome wear safety helmets to minimise risk of injury from drop attacks. The disease is also characterised by intellectual disability, cognitive impairment, behavioural disorders and autism spectrum disorders which are reported in almost half of patients with Lennox-Gastaut syndrome. The condition is also associated with an increased risk of premature mortality.

Cannabidiol is a derivative of the cannabis plant; it does not have psychogenic properties. The precise mechanisms by which it exerts its anticonvulsant effects in humans are unknown. Cannabidiol (Epidyolex®) is formulated as a 100mg/ml solution for oral administration. The recommended starting dose is 2.5mg/kg twice daily (5mg/kg per day) titrating upwards to 10mg/kg per day. Based on individual clinical response and tolerability, each dose can be further increased in weekly increments. The maximum recommended dose is 20mg/kg per day. The Applicant assumed all patients would be prescribed 10mg/kg per day.

It is anticipated that cannabidiol will be prescribed as an adjunctive treatment for patients with Lennox-Gastaut syndrome, who are 2 years of age and older, and who continue to have seizures despite prior treatment with at least two antiepileptic drugs. The place in therapy identified by the Applicant is narrower than the product licence. However, it aligns with clinical opinion and with Department of Health clinical guidelines on medical cannabis,

which state that cannabis-based products are not intended as a first-line treatment option for the disease.

The Applicant identified the relevant comparator to cannabidiol, due to the intractable nature of Lennox-Gastaut syndrome, to be a range of antiepileptic drugs. The basket of antiepileptic drugs, termed 'current clinical management' (CCM) includes clobazam, clonazepam, lacosamide, lamotrigine, levetiracetam, rufinamide, sodium valproate, topiramate, valproic acid and zonisamide, which reflects the established antiepileptic drug regimens that patients were prescribed in the pivotal trials.

1. Comparative effectiveness of cannabidiol

Clinical evidence was derived from two phase-III, randomised, double-blind, placebo-controlled trials, GWPCARE3 (n=225) and GWPCARE4 (n=171). Eligible patients were between 2 and 55 years with a documented history of treatment-refractory Lennox-Gastaut syndrome; had an electroencephalogram that showed a pattern of slow spike-and-wave complexes, which is characteristic of the disorder; and had at least two types of generalised seizure, including drop seizures for at least six months. Patients were also required to have experienced at least two drop seizures each week during the four-week baseline period, and to be prescribed an established antiepileptic regimen consisting of one or more drugs with stable dosing. In GWPCARE3, patients were randomised to either cannabidiol titrated to 10mg/kg per day (n=73), cannabidiol titrated to 20mg/kg per day (n=76), or placebo (n=76). In GWPCARE4, patients were randomised to either cannabidiol titrated to 20mg/kg per day (n=86) or placebo (n=85). The primary endpoint for both studies was percentage change from baseline in drop seizure frequency to the end of the 14-week treatment period, or date of last dose of treatment, whichever occurred first. A key secondary endpoint included the proportion of patients achieving a ≥50% reduction in drop seizure frequency at the end of the treatment period relative to baseline.

In GWPCARE3, the percentage reduction from baseline in drop seizure frequency was 37.2%, 41.9%, and 17.2% for cannabidiol 10mg/kg per day, cannabidiol 20mg/kg per day and placebo, respectively. Percentage reduction from placebo was 19.2% ($p<0.01$) for cannabidiol 10mg/kg per day and 21.6% ($p<0.01$) for cannabidiol 20mg/kg per day. In

GWPCARE4, the percentage reduction from baseline was 43.9% for cannabidiol 20mg/kg per day and 21.8% for placebo [percentage reduction from placebo: 17.2% (p=0.0135)]. Treatment efficacy was more pronounced in the cohort of patients co-prescribed clobazam (which was the subgroup analysis pertaining to the population defined by the product licence). In GWPCARE3, the percentage reduction from baseline in drop seizure frequency was 45.6%, 64.3%, and 22.7% for cannabidiol 10mg/kg per day (n=37), cannabidiol 20mg/kg per day (n=36), and placebo (n=37), respectively [percentage reduction from placebo: 29.6% (p=0.0355) for cannabidiol 10mg/kg per day and 53.8% (p<0.0001) for cannabidiol 20mg/kg per day]. In GWPCARE4, the percentage reduction from baseline was 62.4% for cannabidiol 20mg/kg per day (n=42) compared to 30.7% for placebo (n=42) [percentage reduction from placebo: 45.7% (p<0.0001)].

In GWPCARE3, 35.6%, 39.5% and 14.5% of patients respectively assigned to cannabidiol 10mg/kg per day, cannabidiol 20mg/kg per day and placebo achieved a ≥50% reduction in drop seizure frequency, during the treatment period compared to baseline. The odds ratio (OR) for cannabidiol 10mg/kg per day versus placebo was 3.3 (95% CI 1.5 to 7.3; p<0.01). The OR for cannabidiol 20mg/kg per day versus placebo was 3.9 (95% CI 1.8 to 8.5; p<0.01). In GWPCARE4, 44.2% of patients assigned to cannabidiol 20mg/kg per day and 23.5% of patients assigned to placebo achieved a ≥50% reduction in drop seizure frequency [OR 2.6 (95% CI 1.33 to 4.97; p<0.01)].

GWPCARE5 was an open-label extension study to evaluate the long-term safety and efficacy of cannabidiol. Of 368 patients with Lennox-Gastaut syndrome who completed GWPCARE3 and GWPCARE4, 366 enrolled in GWPCARE5. All patients were titrated to cannabidiol 20mg/kg per day, in addition to their current antiepileptic drug regimen. Investigators could increase (up to 30mg/kg per day) or decrease the dose of cannabidiol; the modal dose of cannabidiol observed in patients with Lennox-Gastaut syndrome during GWPCARE5 was 24mg/kg per day. At three years, cannabidiol continued to demonstrate a reduction in drop seizure frequency similar to that observed in GWPCARE3 and GWPCARE4.

The Review Group had several concerns regarding the clinical evidence and also how it is used for the cost effectiveness assessment, including the short duration of the double-blind

treatment period, the small number of patients informing the treatment efficacy of cannabidiol 10mg/kg per day in combination with clobazam (n=37), and the modal dose (24mg/kg per day) observed in GWPCARE5 was above the maximum daily dose specified in the product licence (20mg/kg per day) and the assumed prescribed dose in the submission (10mg/kg per day). The Review Group also noted that patients included in GWPCARE3 and GWPCARE4 had failed a median of six antiepileptic drugs suggesting a trial population with more treatment-refractory disease compared to that proposed to be treated in Irish clinical practice (patients who have failed two or more antiepileptic drugs).

2. Safety of cannabidiol

The most common adverse reactions associated with cannabidiol are somnolence, decreased appetite, diarrhoea, pyrexia, fatigue and vomiting. The incidence of somnolence is higher in patients prescribed clobazam and cannabidiol in combination. In GWPCARE3 and GWPCARE4, hepatotoxicity was observed more frequently in patients assigned to cannabidiol compared to placebo. Elevations in liver transaminases, more than three times the upper limit of normal, were observed in 4.5% and 18.5% of patients assigned to cannabidiol 10mg/kg per day and cannabidiol 20mg/kg per day, respectively, compared with 0.6% of patients assigned to placebo; the majority of patients were taking concomitant valproate. Elevated liver transaminases were the most common reason for discontinuation from GWPCARE3 and GWPCARE4. In GWPCARE5, elevations in liver transaminases occurred in 13% of patients.

3. Cost effectiveness of cannabidiol

The comparator in the cost-effectiveness evaluation was CCM. A Markov model consisting of states defined by the total number of drop seizures per month and the number of seizure-free days per month was presented. A cycle length of three months was used. In the Applicant's submission, transition probabilities were obtained from the subgroup of patients prescribed clobazam in GWPCARE3 for both the cannabidiol arm and the CCM arm for the first cycle. Patients in the cannabidiol arm followed the transition probabilities from the single arm trial GWPCARE5 for the next eight cycles (two years) of the model. The Review Group are concerned that it may not be realistic to assume that patients would not move between health states for the full 90-year time horizon, especially as all data from

GWPCARE5 (the long term extension study) was not included in the model. The NCPE adjusted base case therefore employed the average transition probabilities from GWPCARE5 for the time horizon of the model. It is a limitation of the model that transition probabilities for the cannabidiol arm were informed solely on a single arm trial, while patients in the CCM arm remained static. However, in the absence of any further data on the CCM arm, the Review Group used the Applicant's assumption that this cohort would remain in their current health state for the rest of the time horizon.

A stopping rule was applied at three pre-specified time points in the model. This was calculated as the percentage of non-withdrawn patients in each health state, who did not achieve a ≥25% reduction in drop seizures, but who did achieve this outcome at the previous time point. The response threshold was based on Department of Health clinical guidelines for cannabis for medicinal use. The Review Group had several concerns regarding application of the stopping rule. A discontinuation rate derived from GWPCARE5 was already applied at these time points, which included patients who stopped treatment due to lack of efficacy. Therefore, we would not expect additional patients to also discontinue due to a lack of efficacy. In addition, the product licence for cannabidiol does not specify that a patient must achieve a particular level of response to be eligible to continue treatment. Clinical opinion to the Review Group indicated that the treatment goal recommended by the Department of Health is considered only a guide; the decision to continue or discontinue a patient's treatment is complex and influenced by multiple factors. In view of these concerns, the Review Group removed the stopping rule in the cost-effectiveness model.

As the payer (HSE), rather than societal perspective, is the recommended approach in Ireland, the review Group adjusted the inclusion of utilities to be in line with the perspective of the HSE. Caregiver utilities have been included as a scenario.

A number of other changes were made in the NCPE adjusted base case. Results of the base case incremental analysis of the costs and outcomes of cannabidiol 10mg/kg per day (in combination with CCM) versus CCM alone are shown in Table 1.

Table 1: Results of the base case incremental analysis – cannabidiol (in combination with CCM) versus CCM

	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)*

Applicant base case	78,112	1.19	65,482
NCPE adjusted base case	95,098	0.98	97,179

QALY: Quality adjusted life year, **ICER:** Incremental cost effectiveness ratio.
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

In the NCPE adjusted base case from the HSE perspective the probability of cannabidiol (in combination with CCM) being cost-effective versus CCM was estimated at 0% at both the €20,000 per QALY and €45,000 per QALY thresholds. In the Applicant's base case from the HSE perspective the probability of cannabidiol (in combination with CCM) being cost-effective versus CCM was estimated at 0% and 0.8% at the €20,000 per QALY and €45,000 per QALY thresholds, respectively. When disutilities from two caregivers are included, the incremental cost-effectiveness ratio (ICER) from the Applicant's model is €24,699 per QALY (incremental costs=78,112, incremental QALY=3.16), while the ICER in the NCPE adjusted base case is €35,941 per QALY (incremental costs=95,098, incremental QALY=2.65).

The licenced maintenance dose for cannabidiol is 10mg/kg per day. However, based on individual clinical response and tolerability, the dose can be further increased up to a maximum recommended dose of 20mg/kg per day. Both the Applicant's and the NCPE adjusted base case assumed that all patients remained on 10mg/kg per day. However, there is a possibility that some patients will be prescribed a higher dose in clinical practice, which would likely increase the ICER of cannabidiol versus CCM.

4. Budget impact of cannabidiol

The price to wholesaler per 100ml bottle of cannabidiol (Epidyolex®) 100mg/ml oral solution is €1,123.66. Medicines for oral administration are not subject to VAT. As cannabidiol is dosed according to patient weight, the monthly and annual cost of treatment will vary between patients. Assuming a maintenance dose of 10mg/kg per day, the estimated cost of treatment per annum to the HSE (incorporating mark-up, 5.5% rebate and patient care fee) for a young patient (2 to approximately 5 years of age) is €8,652; for an adult patient weighing 70kg, the estimated cost of treatment per annum is €30,690.

The Applicant estimated there to be approximately 849 prevalent patients with Lennox-Gastaut syndrome living in Ireland in 2021, and that there would be 41 incident patients per

annum. The Applicant subsequently estimated that 96 patients would be treated with cannabidiol in year one, rising to 253 patients in year four, and decreasing to 252 patients in year five. In calculating these figures, the Applicant assumed market share values for cannabidiol similar to rufinamide; mortality and discontinuation rates were also applied, as was the stopping rule pertaining to treatment response. In view of concerns highlighted above, the Review Group removed the stopping rule from the calculation of estimated patient numbers. The NCPE-adjusted estimate of patients to be treated with cannabidiol was 96 in year one rising to 298 by year five.

Using NCPE-adjusted patient numbers, the gross budget impact for cannabidiol is estimated to be €2.0 million in year one rising to €6.2 million by year five. The cumulative five-year gross budget impact is estimated to be €24.4 million. It is anticipated that cannabidiol will be used as an additional treatment option to current standard of care and that no drugs will be displaced as a result of its introduction. The net budget impact is therefore assumed to be the same as the gross budget impact. Cannabidiol may potentially produce cost-offsets in the form of disease management costs, which could reduce the five-year cumulative budget impact to approximately €22.3 million. Assuming that all patients are prescribed cannabidiol 20mg/kg per day increases the five-year cumulative gross budget impact to approximately €48 million (approximately €46 million incorporating cost offsets); however, these estimates are considered to be conservative.

5. Patient submissions

A patient organisation submission was received during the course of this assessment and this will be provided to the HSE. This submission will form part of the data that the HSE considers.

6. Conclusion

The NCPE recommends that cannabidiol (Epidyolex®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.