Cost-effectiveness of cannabidiol (Epidyolex®)

for use as an adjunctive therapy of seizures associated with Dravet 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 Dravet 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.

Dravet syndrome is a rare, intractable form of severe epilepsy. Convulsive seizures are a characteristic feature of the disease; however, other seizure types are also present. Patients with Dravet syndrome experience significant co-morbidities including intellectual disability, behavioural disorders and motor system dysfunction. 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 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 Dravet 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 Dravet syndrome, to be a range of antiepileptic drugs. The basket of antiepileptic

drugs, termed 'current clinical management' (CCM) includes clobazam, clonazepam, levetiracetam, rufinamide, sodium valproate, stiripentol, 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, GWPCARE1 (n=120) and GWPCARE2 (n=198). Eligible patients were between 2 and 18 years with a documented history of treatment-refractory Dravet syndrome. Patients were also required to have experienced at least four convulsive seizures during the four-week baseline period and to be prescribed an established antiepileptic regimen consisting of one or more drugs with stable dosing. In GWPCARE1 (n=120), patients were randomised to either cannabidiol titrated to 20mg/kg per day (n=61) or placebo (n=59), in addition to the patient's individual established treatment regimen. In GWPCARE2 (n=198), patients were randomised to either cannabidiol titrated to 10mg/kg per day (n=66), cannabidiol titrated to 20mg/kg per day (n=67), or placebo (n=65), in addition to the patient's individual established treatment regimen. The primary endpoint for both studies was percentage change from baseline in total convulsive 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 convulsive seizure frequency at the end of the treatment period relative to baseline.
In GWPCARE1 and GWPCARE2, cannabidiol at both dosing regimens demonstrated statistically significant improvements compared to placebo in reducing convulsive seizure frequency relative to baseline. However, cannabidiol 10mg/kg per day (GWPCARE2) demonstrated numerically superior treatment efficacy compared to cannabidiol 20mg/kg per day (GWPCARE1 and GWPCARE2). In GWPCARE1, the percentage reduction from baseline in convulsive seizure frequency was 38.9%, for cannabidiol 20mg/kg per day and 13.3% for placebo [treatment difference: 22.8% (p=0.01)]. In GWPCARE2, the percentage reduction from baseline in convulsive seizure frequency was 48.7% , 45.7% , and 26.9% for cannabidiol 10mg/kg per day, cannabidiol 20mg/kg per day and placebo, respectively. Percentage reduction from placebo was 29.8% (p<0.01) for cannabidiol 10mg/kg per day and 25.7% (p=0.03) for cannabidiol 20mg/kg per day. 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 GWPCARE1, the percentage reduction from baseline in convulsive seizure frequency was 53.6% for cannabidiol 20mg/kg per day (n=40) compared to 18.9% for placebo (n=38) [treatment difference versus placebo 42.8% (p=0.032)]. In GWPCARE2, the percentage reduction from baseline in convulsive seizure frequency was 60.9%, 56.8%, and 37.6% for cannabidiol 10mg/kg per day (n=45), cannabidiol 20mg/kg per day (n=40), and placebo (n=41), respectively [treatment differences versus placebo: 37.4% (p=0.0042) for cannabidiol 10mg/kg per day and 30.9% (p=0.0297) for cannabidiol 20mg/kg per day].

In GWPCARE1, 42.6% of patients assigned to cannabidiol 20mg/kg per day achieved a ≥50% reduction in convulsive seizure frequency during the treatment period relative to baseline compared to 27.1% of patients assigned to placebo (p=0.08). In GWPCARE2, 43.9%, 49.3% and 26.2% of patients assigned respectively to cannabidiol 10mg/kg per day, cannabidiol 20mg/kg per day and placebo achieved a ≥50% reduction in convulsive seizure frequency (odds ratio (OR) for cannabidiol 10mg/kg per day arm: 2.21 [95% CI 1.06 to 4.62; p=0.03]; OR for cannabidiol 20mg/kg per day: 2.74 [95% CI 1.32 to 5.70; p=0.007]).
GWPCARE5 was an open-label extension study to evaluate the long-term safety and efficacy of cannabidiol. A total of 315 patients with Dravet syndrome who completed GWPCARE1 and GWPCARE2 enrolled in the study. 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 Dravet syndrome during GWPCARE5 was 22mg/kg per day. At 156 weeks, cannabidiol had continued to demonstrate a reduction in convulsive seizure frequency similar to that observed in GWPCARE1 and GWPCARE2.

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=45), the modal dose (22mg/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 GWPCARE1 and GWPCARE2 had failed a median of four 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 GWPCARE1 and GWPCARE2, 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 5% and 19% of patients assigned to cannabidiol 10mg/kg per day and cannabidiol 20mg/kg per day, respectively, compared with 0.8% of patients assigned to placebo; the majority of patients were taking concomitant valproate. Elevated liver transaminases were the most common reason for discontinuation from GWPCARE1 and GWPCARE2. In GWPCARE5, elevations in liver transaminases occurred in 21% of patients and accounted for 5% of discontinuations.

3. Cost effectiveness of cannabidiol

The comparator in the cost-effectiveness evaluation was CCM. As a pharmacoeconomic evaluation of stiripentol for Dravet syndrome was completed in May 2019, the Review Group requested a separate evaluation of cannabidiol versus stiripentol. However, the Applicant declined citing heterogeneity in prescribing for patients with Dravet syndrome in the early stages of treatment as well as differences between the pivotal studies for each drug.

A Markov model consisting of states defined by the total number of convulsive 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 GWPCARE2 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. Patients were assumed to remain in their current health state until

death after the first cycle in the CCM arm, and after the ninth cycle in the cannabidiol arm. 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. 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 for 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 convulsive 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 from 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	63,772	0.65	98,312
NCPE-adjusted base case	80,789	0.34	238,951

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 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 the probability of cannabidiol (in combination with CCM) being cost-effective versus CCM was estimated at 0% and 0.1% 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 €42,503 per QALY (incremental costs = €63,772, incremental QALY=1.5), while the ICER in the NCPE adjusted base case is €102,312 per QALY (incremental costs = €80,789, incremental QALY=0.79).

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 increase the ICER of cannabidiol versus CCM.

4. Budget impact of cannabidiol (Epidyolex®)

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 124 prevalent patients with Dravet syndrome living in Ireland in 2021 and that there would be two incident patients per annum.

The Applicant subsequently estimated that 15 patients would be treated with cannabidiol in year one, rising to 24 patients in year two, and falling to 21 patients in year five. In calculating these figures, the Applicant assumed market share values for cannabidiol similar to stiripentol; 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 estimated 15 patients to be treated with cannabidiol in year one rising to 34 by year four and decreasing to 32 patients by year five.

Using NCPE-adjusted patient numbers, the gross budget impact for cannabidiol is estimated to be €278,744 in year one rising to €633,272 by year four and falling to €603,642 by year five. The cumulative five-year gross budget impact is estimated to be €2.6 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 €2.1 million. Assuming that all patients are prescribed cannabidiol 20mg/kg per day increases the five-year cumulative gross budget impact to approximately €5 million (approximately €4.5 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.