NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Cannabidiol (Epidyolex®) use in adults with Lennox-Gastaut Syndrome, Dravet Syndrome and Tuberous Sclerosis Complex

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

NHS Greater Glasgow and Clyde	**NHS Greater Glasgow and Clyde Neurology** **Protocol for use of Cannabidiol (Epidyolex®) as adjunctive therapy of seizures in adult patients with Lennox Gastaut Syndrome, Dravet Syndrome and Tuberous Sclerosis Complex.**
Background:	Cannabidiol (Epidyolex®) is accepted for use within NHS Scotland for the adjunctive therapy of seizures associated with Lennox-Gastaut Syndrome, Dravet Syndrome, in conjunction with clobazam) and Tuberous Sclerosis Complex (TSC) for patients 2 years of age or older. In the Adult Neurology service this will be patients above the age of 16 years. For other types of epilepsy, there is little or no evidence of benefit and therefore cannabis-based products are not recommended. **Lennox-Gastaut Syndrome** usually begins between 3 and 5 years of age and is characterized by multiple seizure types (predominantly tonic, atonic, and atypical absence seizures), slow EEG spike-waves with abnormal background activity when awake, and fast polyspikes during sleep. Other seizure types may occur including generalised tonic-clonic, focal, and myoclonic seizures and all seizures types may progress to status epilepticus. Drop seizures are common and can lead to physical injury. Cognitive impairment is observed in at least three quarters of patients within 5 years of onset and patients often have behavioural and psychiatric comorbidities. Seizures often continue into adulthood. Patients with Lennox-Gastaut syndrome have an increased risk of death, for example, due to sudden unexpected death in epilepsy (SUDEP). There is no single cause of the disease. However, about two-thirds of patients have an existing neurological condition, for example abnormal development of the brain cortex (cortical dysplasia), congenital infections, stroke, trauma, reduced oxygen supply that occurs before birth (perinatal hypoxia), or infections of the central nervous system such as encephalitis or meningitis. **Dravet Syndrome** is a severe, lifelong condition characterised by seizures beginning in the first year of life, which can be febrile and afebrile, generalised and unilateral, clonic or tonic–clonic. In addition to convulsive seizures, other seizure types appear between the ages of 1 and 4 years, including myoclonic seizures, focal seizures, and atypical absences. Status epilepticus may occur at initial presentation or later in the clinical course. Patients generally have significant developmental delay apparent from the second year of life onwards, with associated neuropsychological disturbances, and almost all patients have intellectual impairment, which is severe in approximately half of them. Dependency in adulthood is usual and death in childhood is common, for example, due to sudden unexpected death in epilepsy (SUDEP). Many patients with Dravet syndrome (70% to 80%) have abnormalities in the sodium channel α1 subunit gene (SCN1A). **Tuberous sclerosis complex** is a rare genetic disorder characterised by growth of noncancerous tumours (known as tubers). Tubers can form in many parts of the body, but most commonly occur in the brain, eyes, kidneys, heart, lungs and skin. Seizures resulting from tubers that have formed in the brain affect up to 85% of people with the condition. Seizures usually start by the age of 2 years as focal onset seizures (which begin in 1 side of the brain) but may progress to generalised seizures

	involving both sides of the brain. Any seizure type is possible (with or without the person retaining consciousness). Drop seizures, in which people lose muscle tone or muscles stiffen, are particularly dangerous and are associated with a risk of injury as people crash to the ground. Tubers that form in the brain can cause a range of cognitive, behavioural, and psychiatric manifestations (known as tuberous sclerosis complex-associated neuropsychiatric disorders or TAND) in around half of people with seizures caused by tuberous sclerosis complex. Severe learning difficulties occur in around 30% of people with tuberous sclerosis complex and may impede speech. Impaired movement may also limit all aspects of daily living. Poor behaviour including anger, mood swings, aggression and a lack of perception of risk often makes daily activities impossible and people may need round-the-clock care. People with the condition also have disrupted sleep, which can impact on the mental health of the entire family. Seizures caused by tuberous sclerosis complex severely affect the quality of life of patients, families and carers.
Agent and route:	100mg /ml oral solution
Patient population applicable to:	Patients with seizures associated with Lennox-Gastaut Syndrome, Dravet Syndrome in conjunction with clobazam treatment, or Tuberous Sclerosis Complex. All patients considered for cannabidiol will be discussed at a complex case / multidisciplinary team meeting.
Indication and place in therapy:	Cannabidiol (Epidyolex®) is accepted for use within NHS Scotland for the adjunctive therapy of seizures associated with Lennox-Gastaut Syndrome, or Dravet Syndrome, in conjunction with Clobazam) in patients above the age of 16 years (in the adult neurology service), and as adjunctive therapy (not specifically with Clobazam) of seizures associated with Tuberous Sclerosis Complex for patients 2 years of age and older. Cannabidiol can be considered if convulsive seizures are not well controlled after trying at least 2 antiepileptic medications **Lennox-Gastaut Syndrome** Lamotrigine, topiramate, rufinamide, and cannabidiol are licensed specifically for the treatment of Lennox-Gastaut syndrome. However, sodium valproate and clobazam are licensed for use in epilepsy and are widely used. Sodium valproate is often used to prevent the initial recurrence of convulsive seizures, and benzodiazepines (for example, diazepam, midazolam, clonazepam, or clobazam) are frequently co-administered to limit the duration of long-lasting seizures. The National Institute of Health and Care Excellence (NICE) guideline recommends for Lennox–Gastaut syndrome first-line treatment with sodium valproate. Lamotrigine is recommended as adjunctive treatment in children, young people and adults if first-line treatment with sodium valproate is unsuitable, ineffective or not tolerated. Other AEDs that may be considered by epilepsy specialists are rufinamide and topiramate. Felbamate (unlicensed medicine) can be also be offered by centres providing tertiary epilepsy specialist care and when treatment with lamotrigine, rufinamide and topiramate has proved ineffective or not tolerated. Polytherapy is common and seizure control is difficult to achieve with current therapies. Clinical experts consulted by SMC note that Lennox-Gastaut syndrome is often refractory to existing AED and there is an unmet need for effective AED to treat this condition.

	Cannabidiol is only licensed for use in conjunction with clobazam. The EMA considers that its therapeutic effects are produced mainly via an interaction that increases clobazam levels about 3-fold. **Dravet Syndrome** Stiripentol is currently the only other medicine licensed in the EU for treatment of Dravet syndrome. Stiripentol is licensed for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with Dravet syndrome whose seizures are not adequately controlled with clobazam and valproate. Fenfluramine is the most recent licensed add-on therapy under SMC restriction where seizures have not been controlled after trying two or more anti-seizure medicines. Fenfluramine can also be offered by centres providing tertiary epilepsy specialist care. In the phase III studies (CARE1 and CARE2), cannabidiol compared with placebo significantly reduced the frequency of convulsive seizures, with a percent change relative to baseline of 23% to 30% over placebo. This was driven mainly by effects in the clobazam-treated subgroup, where the difference over placebo was 31% to 43%. The EMA concluded that efficacy in patients who were not receiving clobazam has not been reliably demonstrated and cannabidiol is therefore only licensed for use in combination with clobazam. The EMA considered that its therapeutic effects are produced mainly via an interaction that increases clobazam levels about 3-fold. The primary outcome was supported by the key secondary outcome, the proportion of patients with at least a 50% reduction in convulsive seizures, and within the clobazam-treated subgroup cannabidiol increased this by 19% to 25% over placebo. **Tuberous Sclerosis Complex** 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 (unlicensed medicine), 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. 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. Everolimus has been accepted for use in NHS Scotland. 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. The evidence to support the use of cannabidiol for TSC-associated seizures comes from one randomised, double-blind, phase III study (GWPCARE6). 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.

Contradindications	Patients with transaminase elevations greater than 3 times the upper limit of normal (ULN) and bilirubin greater than 2 times the ULN.
Dose, duration and administration:	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 maintenance dose of 5mg/kg twice daily (10mg/kg/day). 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). • For patients with Lennox-Gastaut or Dravet syndrome the maximum recommended dose of cannabidiol 10mg/kg twice daily (20mg/kg/day). • For patients with Tuberous Sclerosis Complex the maximum recommended dose of cannabidiol is 12.5mg/kg twice daily (25mg/kg/day). Any dose increases above 10mg/kg/day, up to the maximum recommended dose should be made considering individual benefit and risk and with adherence to the full monitoring schedule (see Intensified Monitoring section). Prescribers may choose a more gradual up-titration for example in two week increments or with a lower starting dose. Consider reducing the dose of clobazam prior to initiation of cannabidiol due to the marked pharmacokinetic drug interaction (see below). If cannabidiol has to be discontinued, the dose should be decreased gradually. Any decision to withhold or stop cannabidiol should be discussed with the respective Consultant. In clinical trials, cannabidiol discontinuation was achieved by reducing the dose by approximately 10% per day for 10 days. A slower or faster down titration may be required, as clinically indicated, at the discretion of the prescriber. Patient may require re-titration if > 7 days therapy missed.
Prescribing	Cannabidiol should be initiated and supervised by neurologists with experience in the treatment of complex epilepsy. Patients must collect supply from the hospital pharmacy department. Epidyolex is not suitable for postage.
Clinically Significant Interactions	The pharmacokinetics of cannabidiol are complex and may cause interactions with the patient's concomitant AED treatments. Cannabidiol and/or concomitant AED treatment should therefore be adjusted during regular medical supervision and the patient should be closely monitored for adverse drug reactions. In addition, monitoring of plasma concentrations should be considered. **Clobazam** Cannabidiol is an anti-epileptic drug (AED) with a mechanism of action that is in part due to a two-way pharmacokinetic interaction with clobazam, which increases by 3-fold the clobazam active metabolite (N-desmethylclobazam) and increases by 1.5 fold the cannabidiol active metabolite (7-hydroxy-cannabidiol). Cannabidiol may have additional effects, but these are not fully characterised and are not produced via cannabinoid receptors. The interaction is bi-directional (i.e. the effects of both the cannabidiol and the clobazam are potentiated). Accumulation of the active N-clobazam metabolite can increase the adverse effects associated with clobazam (i.e. drowsiness, ataxia and irritability) and dose reduction of clobazam may be necessary **Sodium Valproate** Concomitant use of cannabidiol and sodium valproate significantly increases the risk of liver injury. Close monitoring of liver function tests is required. The incidence of

	diarrhoea and decreased appetite appear to be increased when these drugs are used together. The mechanism of this interaction is unknown. **Stiripentol** When cannabidiol was combined with stiripentol in a healthy volunteer trial there was an increase in stiripentol levels of 28% for maximum measured plasma concentration (C_{max}) and 55% for AUC. In patients, however, the effect was smaller, with an increase in stiripentol levels of 17% in C_{max} and 30% in AUC. The clinical importance of these results has not been studied. The patient should be closely monitored for adverse drug reactions. **Phenytoin** Exposure to phenytoin may be increased when it is co-administered with cannabidiol, as phenytoin is largely metabolised via CYP2C9, which is inhibited by cannabidiol *in vitro*. There have not been any clinical studies formally investigating this interaction. Phenytoin has a narrow therapeutic index, so combining cannabidiol with phenytoin should be initiated with caution and if tolerability issues arise, dose reduction of phenytoin should be considered. **Lamotrigine** Lamotrigine is a substrate for UGT enzymes including UGT2B7 which is inhibited by cannabidiol *in vitro*. There have not been any clinical studies formally investigating this interaction. Lamotrigine levels may be elevated when it is co-administered with cannabidiol. **mTOR inhibitors** No dedicated drug-drug interaction studies have been conducted with mTOR inhibitors (e.g., everolimus) or calcineurin inhibitors (e.g., tacrolimus). In view of potential interaction which may lead to increased plasma concentrations of mTOR inhibitors/calcineurin inhibitors, these medications should be co-administered **with caution, and monitoring** of the mTOR/ calcineurin inhibitor blood level should be considered. **Fenfluramine** The manufacturer recommends that no dose adjustment is necessary when fenfluramine is administered with cannabidiol. **Food** Food may increase cannabidiol levels and therefore it should be taken consistently either with or without food, including the ketogenic diet. Other cannabis-based products must not be taken with cannabidiol. **Refer to Summary of Product Characteristics for Epidyolex for full information on drug interactions**
Routine Monitoring	Serum transaminases and total bilirubin levels should be obtained at baseline, 1 month, 3 months, and 6 months after initiation of treatment with cannabidiol, and periodically thereafter or as clinically indicated. More frequent monitoring is required in patients on valproate and with raised baseline transaminases and upon changes in dose above 5mg/kg twice daily). **Monitoring will remain with the acute managed service**
Intensified monitoring	Patients with existing hepatic derangement and patients who are taking valproate should have serum transaminases and total bilirubin levels obtained at weeks 2, 4, 8 and 12, and 6 months after initiation of treatment with cannabidiol, and 6-monthly thereafter or as clinically indicated.

	Upon changes in cannabidiol dose above 10 mg/kg/day or changes in medicinal products (dose change or additions) that are known to impact the liver, this monitoring schedule should be restarted. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction, serum transaminases and total bilirubin should be promptly measured and treatment with cannabidiol should be interrupted or discontinued, as appropriate. Cannabidiol should be discontinued in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN. Patients with sustained transaminase elevations of greater than 5 times the ULN should also have treatment discontinued. Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes. Dose adjustment of any co-administered medicinal product that is known to affect the liver should be considered (e.g., valproate and clobazam).
Monitoring of response	New initiations and reviews of patients receiving cannabidiol will be considered by experienced consultant neurologists as part of a complex case multidisciplinary team meeting The panel will consist of experienced Consultant Neurologists with an interest in epilepsy. **Seizure Diary** A clear indication of seizure frequency, type and duration should be available for at least 3 months, but ideally 6 months before initiating therapy. Consideration should be given to the semiology of the seizure with particular attention given to the risk associated with the seizure type and the influence on Quality of Life. A pre-defined definition of efficacy and a criteria for withdrawing will be agreed prior to drug introduction. This will be considered on a case-to-case basis by the expert panel. **Stopping Criteria** Once reviewed by a neurologist, patients are to stop cannabidiol if the frequency of life threatening seizures has not reduced by at least 50% from baseline at 6 months and review every six months.
Adverse Effects	**Common or very common:** Agitation, appetite abnormal, behaviour abnormal, cough, diarrhoea, drooling, drowsiness, fatigue, fever, increased risk of infection, insomnia, irritability, rash, tremor, vomiting, weight decreased. **Frequency not known** Anaemia, seizure, suicidal tendencies.
Licensed status:	Licensed Medicine: Epidyolex is a Schedule 5 Controlled Drug
Authorised prescribers:	Cannabis-based medicinal products can only be prescribed by Consultant Physicians. In NHS GGC this will be Consultant Neurologists with a specialist interest in Epilepsy
References:	https://www.scottishmedicines.org.uk/medicines-advice/cannabidiol-epidyolex-full-smc2262/ https://www.scottishmedicines.org.uk/medicines-advice/cannabidiol-epidyolex-full-smc2263/ https://www.scottishmedicines.org.uk/medicines-advice/cannabidiol-epidyolex-tsc-full-smc2402/

	https://www.medicines.org.uk/emc/product/10781/smpc
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