Prescribing Information Epidyolex (cannabidiol) 100 mg/ml oral solution

(Please refer to the full Summary of Product Characteristics (SmPC) before prescribing)

PRESENTATION: One 100 ml bottle; each ml contains 100 mg cannabidiol

INDICATIONS: Use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.

Use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older.

Posology / Method of Administration: Should be initiated and supervised by physicians with experience in the treatment of epilepsy.

DOSAGE: Oral solution. Should be taken consistently either with or without food. When taken with food, a similar composition of food should be considered, if possible.

	LGS and DS	**TSC**
Starting dose – first week	2.5mg/kg taken twice daily (5mg/kg/day)	
Second week	Maintenance dose 5mg/kg twice daily (10mg/kg/day)	5mg/kg twice daily (10mg/kg/day)
Further titration as applicable (incremental steps)	Weekly increments of 2.5mg/kg administered twice daily (5mg/kg/day)	
Maximal recommended dose	10mg/kg twice daily (20mg/kg/day)	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.

CONTRAINDICATIONS: Hypersensitivity to the active substance, or to any of the excipients. Transaminase elevations greater than 3 times the upper limit of normal (ULN) and bilirubin greater than 2 times the ULN.

WARNINGS AND PRECAUTIONS: *Hepatocellular injury:* Cannabidiol can cause dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). Prior to starting treatment with cannabidiol, obtain serum transaminases (ALT and AST) and total bilirubin levels. Routine Monitoring - transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment, and periodically 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. Intensified Monitoring - Patients with identified baseline elevations of ALT or AST and patients who are taking valproate should have serum transaminases and total bilirubin levels obtained at 2 weeks, 1 month, 2 months, 3 months, and 6 months after initiation of treatment with cannabidiol, and periodically 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, transaminases and total bilirubin should be promptly measured and treatment should be interrupted or discontinued. 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.

Somnolence and sedation: Can cause somnolence and sedation, more commonly early in treatment and may diminish with continued treatment. The occurrence was higher for those patients on concomitant clobazam. Other CNS depressants, including alcohol, can potentiate the somnolence and sedation effect.

Increased seizure frequency: As with other AEDs, a clinically relevant increase in seizure frequency may occur during treatment with cannabidiol, which may require adjustment in dose of cannabidiol and/or concomitant AEDs, or discontinuation of cannabidiol.

Suicidal behaviour and ideation: Patients should be monitored for signs of suicidal behaviour and ideation and appropriate treatment should be considered.

Decreased weight: Can cause weight loss or decreased weight gain which appeared to be dose-related. Decreased appetite and weight loss may result in slightly reduced height gain. Continuous weight loss/absence of weight gain should be periodically checked to evaluate if cannabidiol treatment should be discontinued.

Sesame oil in the formulation: Contains refined sesame oil which may rarely cause severe allergic reactions.

Benzyl alcohol: Contains 0.0003mg benzyl alcohol which may cause allergic reactions.

Populations not studied: Patients with clinically significant cardiovascular impairment were not included in the TSC clinical development programme.

DRUG INTERACTIONS: *CYP3A4 or CYP2C19 inducers:* Strong inducers of CYP3A4, such as carbamazepine, enzalutamide, mitotane, St. John's wort, and/or strong inducers of CYP2C19, such as rifampin, may decrease plasma concentrations of cannabidiol and decrease the effectiveness of cannabidiol. Dose adjustment may be necessary.

UGT inhibitors: Cannabidiol is a substrate for UGT1A7, UGT1A9 and UGT2B7. No formal drug-drug interaction studies have been conducted with cannabidiol in combination with UGT inhibitors.

Concomitant AED treatments: The pharmacokinetics of cannabidiol are complex and may cause interactions with 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. Monitoring of plasma concentrations should be considered.

Clobazam: When co-administered, bi-directional PK interactions occur. Based on a healthy volunteer study, elevated levels (3- to 4-fold) of N-desmethylclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition, with no effect on clobazam levels. In addition, there was an increased exposure to 7-hydroxy-cannabidiol (7-OH-CBD; an active metabolite of cannabidiol), for which plasma area under the curve (AUC) increased by 47%. Increased systemic levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions. Concomitant use of cannabidiol and clobazam increases the incidence of somnolence and sedation compared with placebo. Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co-administered with cannabidiol.

Valproate: Concomitant use increases the incidence of transaminase enzyme elevations. If clinically significant increases of transaminases occur, cannabidiol and/or concomitant valproate should be reduced or discontinued in all patients until a recovery of transaminase elevations are observed.

Concomitant use of cannabidiol and valproate increases the incidence of diarrhoea and events of decreased appetite.

Stiripentol: When cannabidiol was combined with stiripentol there was an increase in stiripentol levels. Patients 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*. 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*. Lamotrigine levels may be elevated when it is co-administered with cannabidiol.

Mammalian target of rapamycin (mTOR) or calcineurin inhibitors: No dedicated DDI studies have been conducted with mTOR inhibitors (eg. everolimus) or calcineurin inhibitors (eg. tacrolimus). Potential interaction may lead to increased plasma concentration of mTOR inhibitors/calcineurin inhibitors – co-administer with caution, and monitoring of mTOR/calcineurin inhibitor blood level should be considered.

Potential for cannabidiol to affect other medicinal products: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9, and UGT2B7 Substrates - In vitro and *in vivo* (for caffeine) data predict drug-drug interactions with CYP1A2 substrates (e.g., theophylline, caffeine), CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5' diphospho-glucuronosyltransferase 1A9 (UGT1A9) (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 (e.g., gemfibrozil, morphine, lorazepam) when co-administered with cannabidiol. Co-administration of cannabidiol is also predicted to cause clinically significant interactions with CYP2C8 (repaglinide) and CYP2C9 (e.g., warfarin) substrates. *In vitro* data have demonstrated that cannabidiol inhibits CYP2C19, which may cause increased plasma concentrations of medicines that are metabolised by this isoenzyme such as clobazam and omeprazole. Dose reduction should be considered for concomitant medicinal products that are sensitive CYP2C19 substrates or that have a narrow therapeutic index. Because of potential inhibition of enzyme activity, dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, and CYP2C9 should be considered, if adverse reactions are experienced when administered concomitantly with cannabidiol. Because of potential for both induction and inhibition of enzyme activity, dose adjustment of substrates of CYP1A2 and CYP2B6 should be considered. *In vitro assessment of interaction with UGT enzymes - In vitro* data suggest that cannabidiol is a reversible inhibitor of UGT1A9 and UGT2B7-mediated activity at clinically relevant concentrations. The metabolite 7-carboxy-cannabidiol (7-COOH-CBD) is also an inhibitor of UGT1A1, UGT1A4 and UGT1A6-mediated activity *in vitro.* Dose reduction of the substrates may be necessary when cannabidiol is administered concomitantly with substrates of these UGTs.

Ethanol in the formulation: Each ml contains 79mg of ethanol, equivalent to 10% v/v anhydrous ethanol. For an adult weighing 70kg, receiving the maximal single dose (12.5mg/kg), this is equivalent to 17ml of beer, of 7ml of wine per dose.

PREGNANCY AND LACTATION: *Pregnancy:* Should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus. *Breast-feeding:* Breast-feeding should be discontinued during treatment.

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES: Patients should be advised not to drive or operate machinery until they have gained sufficient experience to gauge whether it adversely affects their abilities.

UNDESIRABLE EFFECTS: *Very common:* Decreased appetite, somnolence, sedation, diarrhoea, vomiting, pyrexia, fatigue. *Common:* Pneumonia, urinary tract infection, irritability, aggression,

lethargy, seizure, cough, nausea, AST increased, ALT increased, GGT increased, rash, weight decreased. *Other effects of note:* Decreases in haemoglobin and haematrocrit, elevations in serum creatinine. (Please refer to the full SmPC for further information on side effects).

UK LIST PRICE: 100ml bottle £850.29

LEGAL CATEGORY: POM

MARKETING AUTHORISATION NUMBER GB: PLGB 36772/0001

MARKETING AUTHORISATION HOLDER GB: GW Research Limited, Sovereign House, Vision Park, Chivers Way, Histon, Cambridge CB24 9BZ, United Kingdom

MARKETING AUTHORISATION NUMBER NORTHERN IRELAND: EU/1/19/1389/001

MARKETING AUTHORISATION HOLDER NORTHERN IRELAND: GW Pharma (International) B.V., Databankweg26 3821 AL Amersfoort, The Netherlands.

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GREAT BRITAIN & NORTHERN IRELAND:

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Adverse events should also be reported to GW Pharma on medinfo@gwpharm.com