Prescribing Information for Great Britain.

Epidyolex® (cannabidiol) 100 mg/ml oral solution

Please refer to the Summary of Product Characteristics (SmPC) before making a prescribing decision.

Presentation: One 100 ml bottle; each ml contains 100 mg cannabidiol.

Indication: 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.

Dosage and administration: Should be initiated and supervised by physicians with experience in the treatment of epilepsy. 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. Oral administration is recommended; however, when necessary, nasogastric and gastrostomy tubes may be acceptable routes for enteral administration.

	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 10 mg/kg/day, up to the maximum recommended dose of 25 mg/kg/day should be made considering individual benefit and risk, and with adherence to the full monitoring schedule (see *Warnings and Precautions*).

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Renal impairment: Cannabidiol can be administered to patients with mild, moderate, or severe renal impairment without dose adjustment. There is no experience in patients with end-stage renal disease. It is not known if cannabidiol is dialysable.

Hepatic impairment: Cannabidiol does not require dose adjustment in patients with mild hepatic impairment (Child-Pugh A). Caution should be used in patients with moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C). A lower starting dose is recommended in patients with moderate or severe hepatic impairment. The dose titration should be performed as detailed in the table below.

Hepatic Impairment	**Starting Dose For LGS, DS and TSC**	**Maintenance Dose For LGS and DS**	**Second Week For TSC**	**Maximal Recommended Dose For LGS and DS**	**Maximal Recommended Dose For TSC**
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)		5 mg/kg twice daily (10 mg/kg/day)	6.25 mg/kg twice daily (12.5 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)		2 mg/kg twice daily (4 mg/kg/day)*	2.5 mg/kg twice daily (5 mg/kg/day)*

*Higher doses of cannabidiol may be considered in patients with severe hepatic impairment where the potential benefits outweigh the risks.

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, serum 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 anti-epileptic drugs (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 continued. *Sesame oil in the formulation:* Contains refined sesame oil which may rarely cause severe allergic reactions. *Benzyl alcohol:* Contains 0.0003mg/ml 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.

Interactions: For potential interactions please refer to the information provided in the SmPC.

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.

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Effects on ability to drive and use machines: Cannabidiol has major influence on the ability to drive and operate machines because it may cause somnolence and sedation. 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: ***Please refer to the full SmPC for the complete list of undesirable effects.*** Very common (≥1/10): Decreased appetite, Somnolence, Diarrhoea, Vomiting, Pyrexia, Fatigue, Common (≥1/100 to <1/10) Pneumonia, Urinary tract infection, Irritability, Aggression, Lethargy, Seizure, Cough, Nausea, AST increased, ALT increased, GGT increased, Rash, Weight decreased.

Legal category: POM.

UK List Price: £850.29 (100ml bottle.)

Marketing authorisation number: PLGB 36772/0001.

Marketing Authorisation Holder: Jazz Pharmaceuticals Research UK Limited, Building 730, Kent Science Park, Sittingbourne, Kent ME9 8AG, United Kingdom.

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For the Epidyolex® Summary of Product Characteristics (SmPC); please visit https://www.medicines.org.uk/emc/product/10781

GREAT BRITAIN:

Adverse events should be reported.

Reporting forms and information can be found at:
https://yellowcard.mhra.gov.uk/

Adverse events should also be reported to Jazz Pharmaceuticals by phone: +44 (0)8081890387 (freephone) or by e-mail to medinfo-uk@jazzpharma.com