SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See section 4.8 for advice on the reporting of adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Epidyolex® 100 mg/ml, oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

Cannabidiol

3. PHARMACEUTICAL FORM

Oral solution.
Each ml of solution contains 100 mg cannabidiol (Cannabidiol 100 mg/1 ml).
Clear, colourless to yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 2 years of age and older.

4.2 Posology and method of administration

For LGS and DS Initiation of treatment

The recommended starting dose of Epidyolex is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week.

Maintenance therapy

After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day).

Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day).

Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk and with adherence to the full monitoring schedule (see section 4.4).

For TSC Initiation of treatment

The recommended starting dose of Epidyolex is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week.

Maintenance therapy

After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day) and the clinical response and tolerability should be assessed.

Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 12.5 mg/kg twice daily (25 mg/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 section 4.4).

The dosage recommendations for LGS, DS and TSC are summarised in the following table 1:

Table 1: Dosage recommendations

	LGS and DS	**TSC**
Starting dose – first week	2.5 mg/kg taken twice daily (5 mg/kg/day)	
Second week	Maintenance dose 5 mg/kg twice daily (10 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
Further titration as applicable (incremental steps)	Weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day)	
Maximal recommended dose	10 mg/kg twice daily (20 mg/kg/day)	12.5 mg/kg twice daily (25 mg/kg/day)

Each Epidyolex carton is supplied with:

- Two 1 ml syringes graduated in 0.05 ml increments (each 0.05 ml increment corresponds to 5 mg Epidyolex)
- Two 5 ml syringes graduated in 0.1 ml increments (each 0.1 ml increment corresponds to 10 mg Epidyolex)

If the calculated dose is 100 mg (1 ml) or less, the smaller 1 ml oral syringe should be used. If the calculated dose is more than 100 mg (1 ml), the larger 5 ml oral syringe should be used.

The calculated dose should be rounded to the nearest graduated increment.

Discontinuation

If Epidyolex has to be discontinued, the dose should be decreased gradually. In clinical trials, Epidyolex discontinuation was achieved by reducing the dose by approximately 10% per day for 10 days (see section 4.4). A slower or faster down titration may be required, as clinically indicated, at the discretion of the treating physician.

Combination therapy

Dose adjustments of other medicinal products used in combination with Epidyolex:
A physician experienced in treating patients who are on concomitant antiepileptic drugs (AEDs) should evaluate the need for dose adjustments of Epidyolex or of the concomitant medicinal product(s) to manage potential drug interactions (see sections 4.4 and 4.5).

Special dosage instructions

Patients with hepatic disorders

Epidyolex does not require dose adjustment in patients with mild hepatic impairment (Child-Pugh A).

Caution is required when using Epidyolex in patients with moderate hepatic impairment (Child-Pugh B). Initial-, maintenance-, and maximum dose must be roughly halved compared to that in patients with healthy livers. A maximum dose of more than 10 mg/kg/day for LGS and DS and more than 12.5 mg/kg/day for TSC is not recommended in these patients.

The use of Epidyolex in patients with severely impaired liver function (Child-Pugh C) is not recommended.

(see section 4.4 and 5.2).

Patients with renal disorders

Epidyolex can be administered to patients with mild, moderate, or severe renal impairment without dose adjustment (see section 5.2). There is no experience in patients with end-stage renal disease. It is not known if Epidyolex is dialysable.

Elderly patients

Clinical trials of Epidyolex in the treatment of LGS, DS and TSC did not include a sufficient number of patients aged above 55 years to determine whether or not they respond differently from younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other concurrent therapy (see section 4.4).

Children and adolescents with LGS and DS

There is no relevant use of Epidyolex in children aged below 6 months.

The safety and efficacy of Epidyolex in children aged 6 months to 2 years have not yet been established.

Children and adolescents with TSC

There is no relevant use of Epidyolex in children aged below 1 month.

The safety and efficacy of Epidyolex in children aged 1 month to 2 years have not yet been established.

Delayed administration / Missed doses

In the case of one or more missed doses, the missed doses should not be compensated. Dosing should be resumed according to the existing treatment schedule.

In the case of more than 7 days' missed doses, re-titration to the therapeutic dose should be made.

Mode of administration

Oral use.

Food may increase Epidyolex levels and therefore it should be taken consistently either with or without food, including the ketogenic diet. When taking with food, a similar composition of food should be maintained as far as possible.

Oral administration is recommended; however, when necessary, nasogastric and gastrostomy tubes may be acceptable routes for enteral administration. Tubes made of polyvinyl chloride and polyurethane should not be used (see section 6.6).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- If a patient develops hypersensitivity reactions after treatment with Epidyolex, the medicinal product should be discontinued.
- Patients with transaminase elevations greater than 3 times the upper limit of normal (ULN) and bilirubin greater than 2 times the ULN (see section 4.4).

4.4 Special warnings and precautions for use

Hepatocellular injury

Epidyolex can cause dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) (see section 4.8). The elevations typically occur in the first two months of treatment initiation; however, there were cases observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate.

In clinical trials, the majority of ALT elevations occurred in patients taking concomitant valproate. Concomitant use of clobazam also increased the incidence of transaminase elevations, although to a lesser extent than valproate. Dose adjustment or discontinuation of valproate or clobazam should be considered if transaminase elevations occur.

Regression of transaminase elevations to baseline levels occurred with discontinuation of Epidyolex or reduction of Epidyolex and/or concomitant valproate in about two-thirds of the

cases. In about one-third of the cases, transaminase elevations resolved during continued treatment with Epidyolex, without dose reduction.

Patients with baseline transaminase levels above the ULN had higher rates of transaminase elevations when taking Epidyolex. In some patients, a synergistic effect of concomitant treatment with valproate upon baseline elevated transaminases resulted in a higher risk of transaminase elevations.

In an uncontrolled study in patients in a different non-epilepsy indication, 2 elderly patients experienced elevations of alkaline phosphatase levels above 2 times the ULN in combination with transaminase elevations. The elevations resolved after discontinuation of Epidyolex.

Monitoring

In general, transaminase elevations of greater than 3 times the ULN in the presence of elevated bilirubin without an alternative explanation are an important predictor of severe liver injury. Early identification of elevated transaminase may decrease the risk of a serious adverse event. Patients with elevated baseline transaminase levels above 3 times the ULN, or elevations in bilirubin above 2 times the ULN, should be evaluated prior to initiation of Epidyolex treatment.

Prior to starting treatment with Epidyolex, serum transaminases (ALT and AST), alkaline phosphatase and total bilirubin levels must be obtained.

Serum transaminases (ALT and AST), alkaline phosphatase and total bilirubin levels should be obtained at 2 weeks, 1 month, 2 months, 3 months, and 6 months after initiation of treatment with Epidyolex, and periodically thereafter or as clinically indicated.

Upon changes in Epidyolex 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 Epidyolex should be interrupted or discontinued, as appropriate. Epidyolex 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) (see section 4.5).

Patients with moderate and severe impairment of the liver function (Child-Pugh B and C)

Patients with impaired liver function were not studied in the pivotal clinical trials.
Epidyolex should be used in patients with moderate impairment of the liver function (Child-Pugh B) only after careful consideration of the benefit-risk ratio and under strict monitoring of the liver function parameters and at a reduced dose (see section 4.2).
The use of Epidyolex in patients with severe impairment of the liver function (Child-Pugh C) is not recommended.

Somnolence and sedation

Epidyolex can cause somnolence and sedation, which often occur early on in treatment and may diminish with continued treatment. The occurrence was higher for those patients on concomitant clobazam (see sections 4.5 and 4.8). Other CNS depressants, including alcohol, can potentiate the somnolence and sedation effect.

Pneumonia

An increased risk of pneumonia has been observed with Epidyolex use. In the controlled clinical trials of patients with LGS or DS, 6% of Epidyolex-treated patients had pneumonia, compared to 1% of patients on placebo. In the controlled clinical trial of patients with TSC, 4% of patients had pneumonia, compared with 1% of patients on placebo. The frequency of pneumonia did not appear to be dose related, with 5% of patients on Epidyolex 20 mg/kg/day experiencing pneumonia, compared to 9% of patients on Epidyolex 10 mg/kg/day. The rate of pneumonia was higher in patients taking concomitant clobazam. Prescribers should monitor patients for signs and symptoms of pneumonia, including significant somnolence and sedation.

Increased seizure frequency

As with other AEDs, a clinically relevant increase in seizure frequency may occur during treatment with Epidyolex, which may require adjustment in dose of Epidyolex and/or concomitant AEDs, or discontinuation of Epidyolex, should the benefit-risk ratio be negative.

Suicidal behaviour and ideation

Suicidal behaviour and ideation have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials with AEDs has shown a small increased risk of suicidal behaviour and ideation. The causal mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for Epidyolex.

Patients should be monitored for signs of suicidal behaviour and ideation and appropriate treatment should be considered. Patients and caregivers of patients should be advised to seek medical advice should any signs of suicidal behaviour and ideation emerge.

Ethanol in the formulation

This medicinal product contains 7.9% w/v ethanol (alcohol) (79 mg/ml ethanol equivalent to 10% v/v anhydrous ethanol), i.e., up to 691 mg ethanol per Epidyolex dose (12.5 mg/kg) for an adult weighing 70 kg.
The low quantity of alcohol in this medicinal product has no noticeable effects.

Benzyl alcohol

This medicinal product contains 0.0003 mg/ml benzyl alcohol corresponding to 0.0026 mg per Epidyolex dose (Epidyolex 12.5 mg/kg per dose for an adult weighing 70 kg).
Benzyl alcohol may cause allergic reactions.

There is an increased risk in small children due to accumulation.

Large quantities should only be used with caution and if absolutely necessary, because of the risk of accumulation and toxicity ("metabolic acidosis"), especially for patients with impaired hepatic or renal function, for pregnant and breast-feeding patients.

Refined sesame oil

Epidyolex contains refined sesame oil which may rarely cause severe allergic reactions.

4.5 Interactions with other medicinal products and other forms of interaction

In vitro data

Cannabidiol is a substrate for CYP3A4, CYP2C19, UGT1A7, UGT1A9 and UGT2B7.

In vitro data suggest that cannabidiol is an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9 and UGT2B7-induced activity at clinically relevant concentrations. The metabolite 7-carboxy-cannabidiol (7-COOH-CBD) is an *in vitro* inhibitor of UGT1A1, UGT1A4 and UGT1A6 at clinically relevant concentrations.

Cannabidiol induces the CYP1A2 and CYP2B6 mRNA expression at clinically relevant concentrations.

Inhibition of P-glycoprotein or BCRP-mediated efflux by cannabidiol in the intestine cannot be ruled out.

The metabolite 7-COOH-CBD is a P-gp/MDR1 substrate and has the potential to inhibit BCRP, OATP1B1, OATP1B3, and OAT3.

Cannabidiol and the metabolite 7-OH-CBD are not substrates of P-gp, BCRP, OATP1B1 or OATP1B3.

The metabolite 7-OH-CBD is not an inhibitor of the major renal or hepatic uptake transporters OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, OATP1B1 and OATP1B3. Cannabidiol is not a substrate for or an inhibitor of the brain uptake transporters OATP1A2 and OATP2B1.

Cannabidiol and 7-OH-CBD are not inhibitors of efflux transporter BSEP at clinically relevant plasma concentrations.

The pharmacokinetics of Epidyolex are complex and may cause interactions with the patient's concomitant AED treatments. The dose of Epidyolex and/or concomitant AED treatment should therefore be adjusted as part of regular medical monitoring and the patient should be closely monitored for adverse drug reactions. In addition, monitoring of plasma concentrations should be considered.

The potential for drug-drug interactions with other concomitant AEDs has been assessed in healthy volunteers and patients (750 mg twice daily in healthy volunteers and 20 mg/kg/day in patients) with epilepsy for clobazam, valproate, stiripentol and everolimus.

Although no formal drug-drug interaction studies have been performed for other AEDs, phenytoin and lamotrigine are addressed based on in vitro data. Interactions and dose recommendations with AEDs and other medicines are summarised in the table below.

Table 2: Interactions with other medicinal products

Concomitant Medication	Effect on Plasma Levels Geometric Mean Ratio (90% CI)	Notes and Recommendations
Antiepileptic Drugs (AEDs)		
Valproate	Healthy volunteers CBD AUC_{tau}: 1.05 (0.90, 1.24) CBD C_{max}: 0.74 (0.58, 0.93) 7-OH-CBD AUC_{tau}: 1.22 (0.96, 1.55) 7-OH-CBD C_{max}: 0.97 (0.67, 1.41) Valproate AUC_{tau}: 0.99 (0.90, 1.08) Valproate C_{max}: 1.01 (0.95, 1.07) Patients Valproat AUC_{tau}: 0.83 (0.75, 0.92) Valproat C_{max}: 0.87 (0.79, 0.95) 4-ene-VPA AUC_{tau}: 0.70 (0.62, 0.80) 4-ene-VPA C_{max}: 0.77 (0.66, 0.90)	Concomitant use of Epidyolex and valproate increases the incidence of transaminase enzyme elevations (see section 4.4). The mechanism of this interaction remains unknown. If clinically significant increases of transaminases occur, cannabidiol and/or valproate should be simultaneously reduced or discontinued in all patients until a recovery of transaminase elevations are observed (see section 4.4). Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic medicinal products and cannabidiol (see section 4.4). Concomitant use of Epidyolex and valproate increases the incidence of diarrhoea and events of decreased appetite. The mechanism of this interaction is unknown. There are no clinically important pharmacokinetic changes in either CBD or VPA or their metabolites.
Clobazam	CBD AUC_{tau}: 1.30 (1.00, 1.70) CBD C_{max}: 1.34 (0.93, 1.95) 7-OH-CBD AUC_{tau}: 1.47 (1.26, 1.70) 7-OH-CBD C_{max}: 1.73 (1.36, 2.20) Clobazam AUC_{tau}: 1.06 (0.90, 1.24) to 1.21 (1.05, 1.39) Clobazam C_{max}: 1.00 (0.83, 1.19) to 1.20 (1.05, 1.38) N-CLB AUC_{tau}: 2.64 (1.95, 3.58) to 3.38 (2.62, 4.36) N-CLB C_{max}: 2.22 (1.42, 3.46) to 3.39 (2.61, 4.39)	Concomitant use of Epidyolex and clobazam increases the incidence of somnolence and sedation (see sections 4.4 and 4.8). Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co-administered with Epidyolex. When Epidyolex and clobazam are co-administered there are no effects on cannabidiol or clobazam plasma levels, however bi-directional PK interactions occur affecting their active metabolites (N-desmethylclobazam and 7-hydroxy cannabidiol). Increased systemic plasma levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions. Therefore, dose adjustments of Epidyolex or clobazam may be required.

Concomitant Medication	**Effect on Plasma Levels Geometric Mean Ratio (90% CI)**	**Notes and Recommendations**
Stiripentol	Healthy volunteers CBD AUC_{tau}: 1.03 (0.94, 1.14) CBD C_{max}: 1.13 (0.96, 1.33) 7-OH-CBD AUC_{tau}: 0.72 (0.61, 0.85) 7-OH-CBD C_{max}: 0.71 (0.51, 0.99) Stiripentol AUC_{tau}: 1.55 (1.42, 1.69) Stiripentol C_{max}: 1.28 (1.08, 1.52) Patients Stiripentol AUC_{tau}: 1.30 (1.09, 1.55) Stiripentol C_{max}: 1.17 (1.03, 1.33)	When Epidyolex was combined with stiripentol administration there was a minor increase in stiripentol plasma levels. The clinical relevance of this is unknown, but the patient should be closely monitored for adverse drug reactions. There is no effect on cannabidiol plasma levels. The interaction resulted in a decrease (approximately 30%) in C_{max} and AUC of the active metabolite, 7-OH-CBD, in healthy volunteer trials.
Phenytoin	A potential drug-drug interaction has not been studied.	Exposure to phenytoin may be increased when it is co-administered with Epidyolex, as phenytoin is largely metabolised via CYP2C9, which is inhibited by cannabidiol *in vitro*. Phenytoin has a narrow therapeutic index, so combining Epidyolex with phenytoin should be initiated with caution and if tolerability issues arise, dose reduction of phenytoin should be considered.
Lamotrigine	A potential drug-drug interaction has not been studied.	Lamotrigine is a substrate for UGT enzymes including UGT2B7, which is inhibited by cannabidiol *in vitro*. Lamotrigine plasma levels may be elevated when it is co-administered with Epidyolex.
Everolimus	Everolimus $AUC_{0-\infty}$: 2.45 (2.15, 2.80) Everolimus C_{max}: 2.50 (2.12, 2.94)	Concomitant use of Epidyolex (12.5 mg/kg twice daily) and everolimus (5 mg), a P-glycoprotein (P-gp) and CYP3A4 substrate, led to an increase in everolimus exposure. The half-life of everolimus was not affected. When initiating Epidyolex in patients taking everolimus, monitor therapeutic drug levels of everolimus and adjust the dosage accordingly. When initiating everolimus in patients taking a stable dosage of Epidyolex, a lower starting dose of everolimus is recommended, with therapeutic drug monitoring. Increases in exposure of other orally administered P-gp substrates (e.g., sirolimus, tacrolimus, digoxin) may be observed on coadministration with Epidyolex. Therapeutic drug monitoring and dose reduction of other P-gp substrates should be considered when given orally and concurrently with Epidyolex. The dosage recommendations in the information for health care professionals for the respective medicinal products must be observed.

Concomitant Medication	Effect on Plasma Levels Geometric Mean Ratio (90% CI)	Notes and Recommendations
CYP2C19 Substrates / Inhibitors		
Fluconazole	CBD AUC_t: 1.21 (1.08, 1.36) CBD C_{max}: 1.24 (1.05, 1.47) 7-OH-CBD AUC_t: 0.71 (0.61, 0.82) 7-OH-CBD C_{max}: 0.59 (0.48, 0.72) The effect on fluconazole has not been studied.	Fluconazole, a potent CYP2C19 inhibitor, has only a minor effect on CBD exposure and causes a small decrease in 7-OH-CBD exposure. None of these changes are considered clinically meaningful. Epidyolex may cause increased plasma concentrations of medicines that are metabolised by CYP2C19, e.g., omeprazole and clobazam (see above). Dose reduction should be considered for concomitant medicinal products that are sensitive CYP2C19 substrates, or that have a narrow therapeutic index.
CYP2C19 Inducers		
Rifampicin	CBD AUC_t: 0.68 (0.61, 0.75) CBD C_{max}: 0.66 (0.56, 0.78) 7-OH-CBD AUC_t: 0.37 (0.33, 0.41) 7-OH-CBD C_{max}: 0.33 (0.29, 0.38) The effect on rifampicin has not been studied.	Rifampicin and other strong inducers of CYP2C19 may decrease the plasma concentration of cannabidiol and therefore decrease the effectiveness of Epidyolex.
CYP3A4 Substrates / Inhibitors		
Midazolam	Midazolam AUC_t: 0.92 (0.78, 1.09) Midazolam C_{max}: 0.80 (0.67, 0.96) 1'-hydroxymidazolam AUC_t: 1.68 (1.41, 2.01) 1'-hydroxymidazolam C_{max}: 1.12 (0.93, 1.34) The effect on cannabidiol has not been studied.	Epidyolex has no effect on the clearance of midazolam and is not expected to affect clearance of other sensitive CYP3A4 substrates.
Itraconazole	CBD AUC_t: 1.05 (0.96, 1.15) CBD C_{max}: 1.01 (0.82, 1.25) 7-OH-CBD AUC_t: 1.17 (1.07, 1.27) 7-OH-CBD C_{max}: 1.06 (0.90, 1.25) The effect on itraconazole has not been studied.	Itraconazole, a potent CYP3A4 inhibitor, does not affect CBD exposure and causes a very small, clinically insignificant increase in 7-OH-CBD exposure.
CYP3A4 Inducers		
e.g., rifampicin, carbamazepine, enzalutamide, mitotane, St. John's wort	See rifampicin study data (CYP2C19 Inducers)	Strong inducers of CYP3A4 may decrease the plasma concentration of cannabidiol and therefore decrease the effectiveness of Epidyolex. Dose adjustment may be necessary.

Concomitant Medication	Effect on Plasma Levels Geometric Mean Ratio (90% CI)	Notes and Recommendations
CYP2C8 and CYP2C9 Substrates / Inhibitors		
e.g., repaglinide, warfarin	A potential drug-drug interaction has not been studied.	Dose reduction of substrates of CYP2C8 and CYP2C9 should be considered, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with Epidyolex.
CYP1A2 Substrates / Inhibitors		
e.g., theophylline, caffeine	Caffeine AUC_t: 1.88 (1.56, 2.27) Caffeine C_{max}: 1.15 (1.04, 1.26)	These data indicate that Epidyolex is a weak inhibitor of CYP1A2. Similar modest increases in exposure may be observed with other sensitive CYP1A2 substrates (e.g., theophylline or tizanidine). Dose adjustment of substrates of CYP1A2 should be considered, as clinically appropriate. The dosage recommendations in the information for health care professionals for the respective medicinal products must be observed.
CYP2B6 Substrates / Inhibitors		
e.g., bupropion, efavirenz	A potential drug-drug interaction has not been studied.	Dose adjustment of substrates of CYP2B6 should be considered, as clinically appropriate.
UGT1A7, UGT1A9, and UGT2B7 Substrates / Inhibitors		
e.g., diflunisal, propofol, fenofibrate, gemfibrozil, morphine, lorazepam	A potential drug-drug interaction has not been studied.	Dose reduction of substrates of UGT1A7, UGT1A9, and UGT2B7 or of Epidyolex should be considered, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with Epidyolex.
UGT1A1, UGT1A4 and UGT1A6 Substrates / Inhibitors		
e.g., lamotrigine, olanzapine, paracetamol	A potential drug-drug interaction has not been studied.	The metabolite 7-COOH-CBD is an inhibitor of UGT1A1, UGT1A4 and UGT1A6-mediated activity *in vitro*. Dose reduction of the substrates may be necessary when Epidyolex is administered concomitantly with substrates of these UGTs.
P-gp substrates / Inhibitors (orally administered)		
e.g., sirolimus, tacrolimus, digoxin	See AEDs, everolimus	
Oral Contraceptives		
e.g., ethinylestradiol, levonorgestrel	A potential drug-drug interaction has not been studied.	Cannabidiol is not an inducer of CYP3A4 and therefore is not expected to alter the pharmacokinetics of hormonal contraceptives.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are only very limited data from the use of Epidyolex in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Epidyolex should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

Lactation

There are no clinical data on the presence of Epidyolex or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

Studies in animals have shown toxicological changes in lactating animals, when the mother was treated with cannabidiol (see section 5.3).

Given that cannabidiol is highly protein bound and will likely pass freely from plasma into milk, breast-feeding should be discontinued during treatment.

Fertility

No data on the effects of Epidyolex on human fertility are available.

No effect on reproductive ability of male or female rats was noted with an oral dose of up to 150 mg/kg/day cannabidiol (see section 5.3).

4.7 Effects on ability to drive and use machines

Epidyolex has major influence on the ability to drive and operate machines because it may cause somnolence and sedation (see section 4.4). Patients should be advised not to drive or operate machinery until they have gained sufficient experience to gauge whether it adversely affects their abilities (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions reported with Epidyolex in the recommended dose range of 10 to 25 mg/kg/day are shown below.

The most common adverse reactions are somnolence, decreased appetite, diarrhoea, pyrexia, fatigue, and vomiting.

The most frequent cause for treatment discontinuations was transaminase elevation.

Adverse reactions reported with Epidyolex in placebo-controlled clinical studies are listed below by System Organ Class and frequency.

The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Pneumonia[a], Urinary tract infection
Metabolism and nutrition disorders	Very common	Decreased appetite (21%)
Psychiatric disorders	Common	Irritability, Aggression
Nervous system disorders	Very common	Somnolence[a] (26%)
	Common	Lethargy, Seizure
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very common	Diarrhoea (24%), Vomiting (13%)
	Common	Nausea
Hepatobiliary disorders	Common	AST increased, ALT increased, GGT increased
Skin and subcutaneous tissue disorders	Common	Rash
General disorders and administration site conditions	Very common	Pyrexia (16%), Fatigue (10%)
Investigations	Common	Weight decreased

[a] Grouped Terms: **Pneumonia:** Pneumonia, RSV pneumonia, Mycoplasma pneumonia, Adenovirus pneumonia, Viral pneumonia, Aspiration pneumonia; **Somnolence:** Somnolence, Sedation.

Description of selected adverse reactions

Hepatocellular injury

Epidyolex can cause dose-related elevations of ALT and AST values (see section 4.4).

In controlled studies for LGS, DS (receiving 10 or 20 mg/kg/day) and for TSC (receiving 25 mg/kg/day), the incidence of ALT elevations above 3 times the ULN was 12% in Epidyolex-treated patients compared with ≤ 1% in patients on placebo. Less than 1% of Epidyolex-treated patients had ALT or AST levels greater than 20 times the ULN. There have been cases of transaminase elevations associated with hospitalisation in patients taking Epidyolex.

Risk factors for hepatocellular injury

Concomitant administration of valproate and clobazam, dose of Epidyolex and baseline transaminase elevations.

Concomitant administration of valproate and clobazam

In Epidyolex-treated patients receiving doses of 10, 20, and 25 mg/kg/day, the incidence of ALT elevations greater than 3 times the ULN was 23% in patients taking both concomitant valproate and clobazam, 19% in patients taking concomitant valproate (without clobazam), 3% in patients taking concomitant clobazam (without valproate), and 3% in patients taking neither drug.

Dose

ALT elevations greater than 3 times the ULN were reported in 15% of patients taking Epidyolex 20 or 25 mg/kg/day compared with 3% of patients taking Epidyolex 10 mg/kg/day. The risk of ALT elevations was higher at dosages higher than the 25 mg/kg/day in the controlled study in TSC.

Baseline transaminase elevations

In controlled trials (see section 5.1) in patients taking Epidyolex 20 or 25 mg/kg/day, the frequency of ALT elevations greater than 3 times the ULN was 29% (80% of these were on valproate) when ALT was above the ULN at baseline, compared to 12% (89% of these were on valproate) when ALT was within the normal range at baseline. A total of 5% of patients (all on valproate) taking Epidyolex 10 mg/kg/day experienced ALT elevations greater than 3 times the ULN when ALT was above the ULN at baseline, compared with 3% of patients (all on valproate) in whom ALT was within the normal range at baseline.

Somnolence and sedation

Somnolence and sedation (including lethargy) events have been observed in controlled trials with Epidyolex in LGS, DS, and TSC, including 29% of Epidyolex-treated patients (30% of patients taking Epidyolex 20 or 25 mg/kg/day and 27% of patients taking Epidyolex 10 mg/kg/day). These adverse reactions were observed at higher incidences at dosages above 25 mg/kg/day in the controlled study in TSC. The rate of somnolence and sedation (including lethargy) was higher in patients on concomitant clobazam (43% in Epidyolex-treated patients taking clobazam, compared with 14% in Epidyolex-treated patients not on clobazam).

Decreased weight

Epidyolex can cause weight loss or decreased weight gain. In LGS, DS and TSC patients, the decrease in weight appeared to be dose-related, with 21% of patients on Epidyolex 20 or 25 mg/kg/day experiencing a decrease in weight of $\geq$ 5%, compared to 7% in patients on Epidyolex 10 mg/kg/day and 8% in patients on placebo. In some cases, the decreased weight was reported as an adverse event (see the list above). 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 Epidyolex treatment should be continued.

Haematologic abnormalities

Epidyolex can cause decreases in haemoglobin and haematocrit. In LGS, DS, and TSC patients, the mean decrease in haemoglobin from baseline to end of treatment was −0.36 g/dL in Epidyolex treated patients receiving 10, 20, or 25 mg/kg/day and 0.20 g/dL in patients on placebo. A corresponding decrease in haematocrit was also observed, with a mean change of −1.3% in Epidyolex treated patients and -0.3% in patients on placebo.
There was no effect on red blood cell indices. Twenty seven percent (27%) of Epidyolex treated patients with LGS and DS and 38% of Epidyolex-treated patients (25 mg/kg/day) with TSC developed a new laboratory defined anaemia during the course of the study (defined as a normal haemoglobin concentration at baseline, with a reported value less than the lower limit of normal at a subsequent time point) versus 14% of patients with LGS and DS on placebo and 15% of patients with TSC on placebo.

Increases in creatinine

Epidyolex can cause elevations in serum creatinine. The mechanism has not yet been determined. In controlled studies in healthy adults and in patients with LGS, DS and TSC an increase in serum creatinine of approximately 10% was observed within 2 weeks of starting Epidyolex. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS, DS or TSC.

To report any side effect(s):

Kingdom of Saudi Arabia:
The National Pharmacovigilance Centre (NPC):
SFDA Call Center: 19999
e-mail: npc.drug@sfda.gov.sa
website: http://ade.sfda.gov.sa

United Arab Emirates:
Pharmacovigilance & Medical Device section
Emirates Drug Establishment
United Arab Emirates
Email: pv@ede.gov.ae
Tel: 80033784

Kuwait:
Kuwait Ministry of Health Drug and Food
Control Pharmaceutical and Herbal
Medicines Registration and Control Administration
Phone: +965 (4829287-24847475)
Fax: +965 24847477
E-Mail: ADR_reporting@moh.gov.kw

Other GCC States:
Please contact the relevant competent authority.

4.9 Overdose

Signs and symptoms

Experience with doses higher than the recommended therapeutic dose is limited. Mild to moderate diarrhoea and somnolence have been reported in healthy adult subjects taking a single dose of 6000 mg; this equates to a dose of over 85 mg/kg for a 70 kg adult. These adverse reactions resolved upon study completion.

Treatment

In the event of overdose the patient should be observed and appropriate symptomatic treatment given, including monitoring of vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N03AX24.

Mechanism of action

The precise mechanisms by which cannabidiol exerts its anticonvulsant effects in humans are unknown.

Cannabidiol does not exert its anticonvulsant effect through interaction with cannabinoid receptors.

Cannabidiol reduces neuronal hyper-excitability through modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid subtype 1 (TRPV-1) channels, as well as modulation of adenosine-mediated signalling through inhibition of adenosine intracellular uptake via the equilibrative nucleoside transporter 1 (ENT-1).

Cardiac Electrophysiology

In a randomized, placebo- and positive-controlled, parallel, multiple-dose study in which healthy adult subjects were titrated to a dose 3 to 4 times the maximum recommended dose (40 mg/kg administered under fed conditions), CBD-OS did not prolong the QTc interval to a clinically relevant extent at the expected therapeutic exposure. A prolongation of the QTc interval cannot be excluded in the case of supratherapeutic exposure.

Clinical efficacy

Adjunctive therapy in patients with Lennox-Gastaut syndrome (LGS)

The efficacy of Epidyolex for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) was evaluated in two randomised, double-blind, placebo-controlled, parallel-group studies (GWPCARE3 and GWPCARE4). Each study consisted of a 4-week baseline period, a 2-week titration period and a 12-week maintenance period. Mean age of the study population was 15 years and 94% were taking 2 or more concomitant AEDs (cAEDs)

during the trial. The most commonly used cAEDs (> 25% of patients) in both trials were valproate, clobazam, lamotrigine, levetiracetam, and rufinamide.

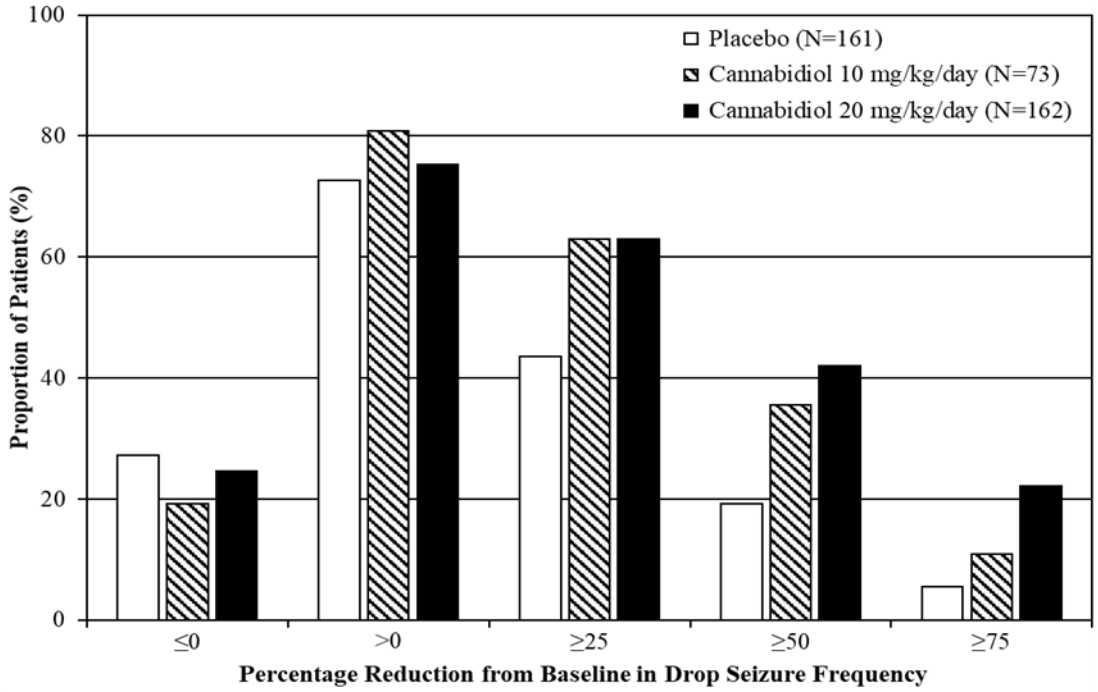
The primary endpoint was the percentage change from baseline in drop seizures per 28 days over the treatment period for the Epidyolex group compared to placebo. Drop seizures were defined as atonic, tonic, or tonic-clonic seizures. Key secondary endpoints were the proportion of patients with at least 50% reduction in drop seizure frequency, the percentage change from baseline in total seizure frequency, and Patient/Caregiver Global Impression of Change at the last visit. These outcome measures are summarized in Table 3.

Table 3: Primary and key secondary outcome measures in LGS studies

	Study GWPCARE3			***Study*** GWPCARE4	
	Epidyolex **20 mg/kg/day** (n = 76)	**Epidyolex** **10 mg/kg/day** (n = 73)	**Placebo** (n = 76)	**Epidyolex** **20 mg/kg/day** (n = 86)	**Placebo** (n = 85)
Primary endpoint – Percentage reduction in drop seizure frequency					
Drop seizures **Median % Reduction**	41.9	37.2	17.2	43.9	21.8
Comparison to Placebo **Difference**	21.6	19.2		17.2	
95% CI	6.7; 34.8	7.7; 31.2		4.1; 30.3	
P-value	0.005	0.002		0.014	
Key secondary endpoints					
50% responder proportion[a]	39.5%	35.6%	14.5%	44.2%	23.5%
P-value	0.001	0.003		0.004	
Total seizures **Median % Reduction**	38.4	36.4	18.5	41.2	13.7
Comparison to Placebo **Difference**	18.8	19.5		21.1	
95% CI	4.4; 31.8	7.5; 30.4		9.4; 33.3	
P-value	0.009	0.002		0.001	
Mean P/CGIC results (last visit)	3.2 (sl. improved)	3.0 (sl. improved)	3.6 (no change)	3.0 (sl. improved)	3.7 (no change)
P-value	0.044	0.002		0.001	

CI=95% confidence interval; Difference = treatment difference (12 weeks); a=proportion of patients with at least 50% reduction in drop seizure frequency; sl.=slightly.

Figure 1: Cumulative Proportion of Patients by Category of Seizure Response in the Treatment Period for Cannabidiol and Placebo in Patients with Lennox-Gastaut Syndrome (GWPCARE3 and GWPCARE 4)



Epidyolex was associated with an increase in the number of drop seizure-free days during the treatment period in each trial, equivalent to an additional 3-5 days per 28 days versus placebo (20 mg/kg/day) and an additional 3 days per 28 days versus placebo (10 mg/kg/day).

Adjunctive Therapy in Patients with Dravet Syndrome

The efficacy of Epidyolex for the adjunctive therapy of seizures associated with Dravet syndrome (DS) was evaluated in two randomised, double-blind, placebo-controlled, parallel-group studies (GWPCARE2 and GWPCARE1). Each study consisted of a 4-week baseline period, a 2-week titration period and a 12-week maintenance period. Mean age of the study population was 9 years and 94% were taking 2 or more cAEDs during the trial. The most commonly used cAEDs (> 25% of patients) in both trials were valproate, clobazam, stiripentol, and levetiracetam.

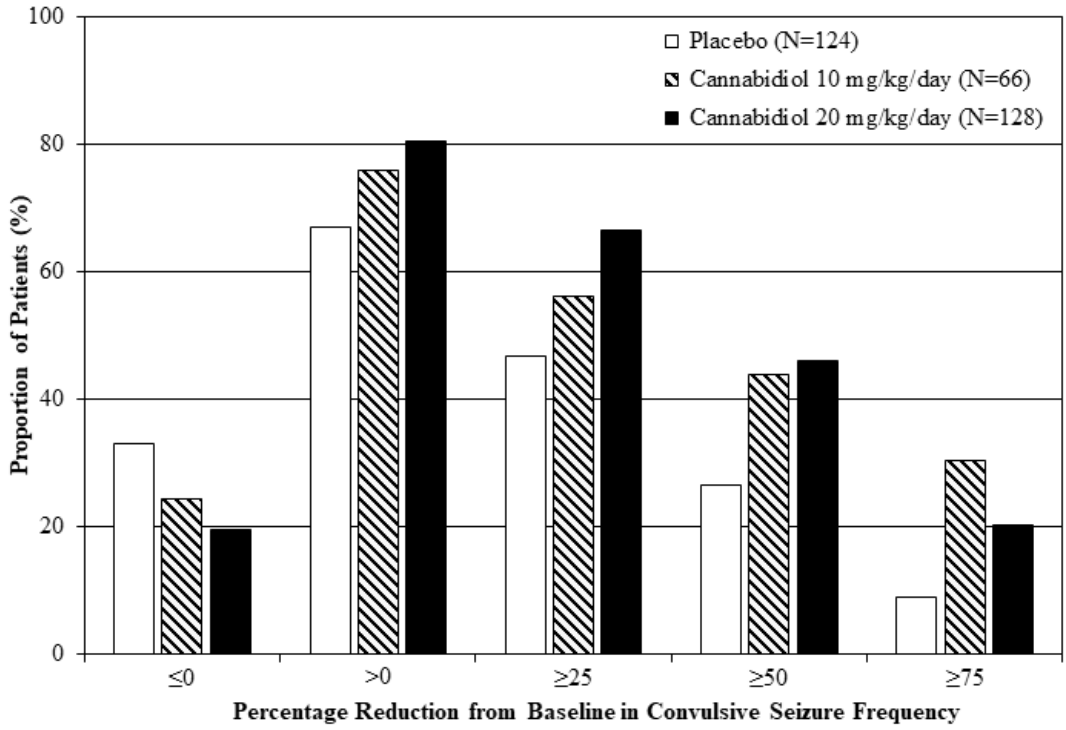
The primary endpoint was the change in convulsive seizure frequency during the treatment period (Day 1 to the end of the evaluable period) compared to baseline (GWPCARE2), and the median percentage change in convulsive seizures per 28 days over the treatment period for the Epidyolex group compared to placebo (GWPCARE1). Convulsive seizures were defined as all countable atonic, tonic, clonic, and tonic-clonic seizures. Key secondary endpoints for GWPCARE2 were the proportion of patients with at least 50% reduction in convulsive seizure frequency, the change in total seizure frequency, and Caregiver Global Impression of Change at the last visit. The key secondary endpoint for GWPCARE1 was the proportion of patients with at least 50% reduction in convulsive seizure frequency. These outcome measures are summarised in Table 4.

Table 4: Primary and key secondary outcome measures in DS studies

	Study GWPCARE2			***Study*** GWPCARE1	
	Epidyolex 20 mg/kg/day (n = 67)	**Epidyolex 10 mg/kg/day** (n = 66)	**Placebo** (n = 65)	**Epidyolex 20 mg/kg/day** (n = 61)	**Placebo** (n = 59)
Primary endpoint	***Reduction in convulsive seizure frequency***			***Percentage reduction in convulsive seizure frequency***	
Convulsive seizures **Median % Reduction/ % Reduction**	45.7	48.7	26.9	38.9	13.3
Comparison to Placebo **% Reduction**	25.7	29.8		22.8	
Difference 95% CI	2.9; 43.2	8.4; 46.2		5.4; 41.1	
P-value	0.030	0.010		0.012	
Key secondary endpoints					
50% responder proportion [a]	49.3%	43.9%	26.2%	42.6%	27.1%
P-value	0.007	0.033		0.078	
Total seizures **Median % Reduction/ % Reduction**	47.3	56.4	29.7	*	
Comparison to Placebo **% Reduction**	25.1	38.0			
Difference 95% CI	3.5; 41.9	20.1; 51.9			
P-value	0.026	<0.001			
Mean P/CGIC results (last visit)	3.1 (sl. improved)	2.8 (sl. improved)	3.6 (no change)	*	
P-value	0.028	0.001			

CI=95% confidence interval; Difference=treatment difference (12 weeks); a=proportion of patients with at least 50% reduction in convulsive seizure frequency; sl.=slightly.
* For study GWPCARE1, total seizures and CGIC endpoints were not included in formal hypothesis testing and hence results are not shown.

Figure 2: Cumulative Proportion of Patients by Category of Seizure Response in the Treatment Period for Epidyolex and Placebo in Patients with Dravet Syndrome (GWPCARE2 and GWPCARE1)



Placebo (n=124); Cannabidiol 10 mg/kg/day (n=66); Cannabidiol 20 mg/kg/day (n=128); Proportion of patients (%)

Epidyolex was associated with an increase in the number of convulsive seizure-free days during the treatment period in each trial, equivalent to an additional 1,3 to 1.4 days per 28 days versus placebo (20 mg/kg/day) and an additional 2.4 days per 28 days versus placebo (10 mg/kg/day).

Adult population

The DS population in studies GWPCARE2 and GWPCARE1 was predominantly paediatric patients, with only 5 adult patients who were 18 years old (1.6%), and therefore limited efficacy and safety data were obtained in the adult DS population.

Dose response

Given that there was no consistent dose response between 10 mg/kg/day and 20 mg/kg/day in the LGS and DS studies (see Figures 1 and 2), Epidyolex should be titrated initially to the recommended maintenance dose of 10 mg/kg/day (see section 4.2). In individual patients, titration up to a maximum dose of 20 mg/kg/day may be considered, based on the benefit-risk (see section 4.2).

Open-label data

Across both randomised LGS studies, 99.5% of patients who completed the studies were enrolled into the long-term open-label extension study (GWPCARE5). In this study, in patients with LGS treated for 37 to 48 weeks (N=299), the median percentage reduction from

baseline in drop seizure frequency was 55% during Week 1–12, which was maintained through to Week 37–48 (60%).

Across both randomised DS studies, 97.7% of patients who completed the studies were enrolled into GWPCARE5. In this study, in patients with DS treated for 37 to 48 weeks (N=214), the mean percentage reduction from baseline in convulsive seizure frequency was 56% during Week 1–12, which was maintained through to Week 37–48 (54%).

Adjunctive therapy in patients with tuberous sclerosis complex (TSC)

The efficacy of Epidyolex (25 and 50 mg/kg/day) for the adjunctive therapy of seizures associated with TSC was evaluated in a randomised, double-blind, placebo-controlled, parallel-group study (GWPCARE6). The study consisted of a 4-week baseline period, a 4-week titration period and a 12-week maintenance period (16-week treatment and primary evaluation period).

Mean age of the study population was 14 years and all patients but one were taking one or more concomitant AEDs (cAEDs) during the study. The most commonly used cAEDs (> 25% of patients) were valproate (45%), vigabatrin (33%), levetiracetam (29%), and clobazam (27%).

The primary endpoint was the change in number of TSC-associated seizures during the treatment period (maintenance and titration) compared to baseline for the Epidyolex group compared to placebo. TSC-associated seizures were defined as focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic seizures). Key secondary endpoints were the proportion of patients with at least a 50% reduction in TSC-associated seizure frequency, Subject/Caregiver Global Impression of Change at the last visit and the percentage change from baseline in total seizure frequency.

Epidyolex 50 mg/kg/day was shown to have a similar level of seizure reduction as 25 mg/kg/day. However, this dose was associated with an increased rate of adverse reactions compared to the 25 mg/kg/day and therefore the maximum recommended dose is 25 mg/kg/day.

Table 5 summarises the outcome measures for the maximum recommended dose of 25 mg/kg/day.

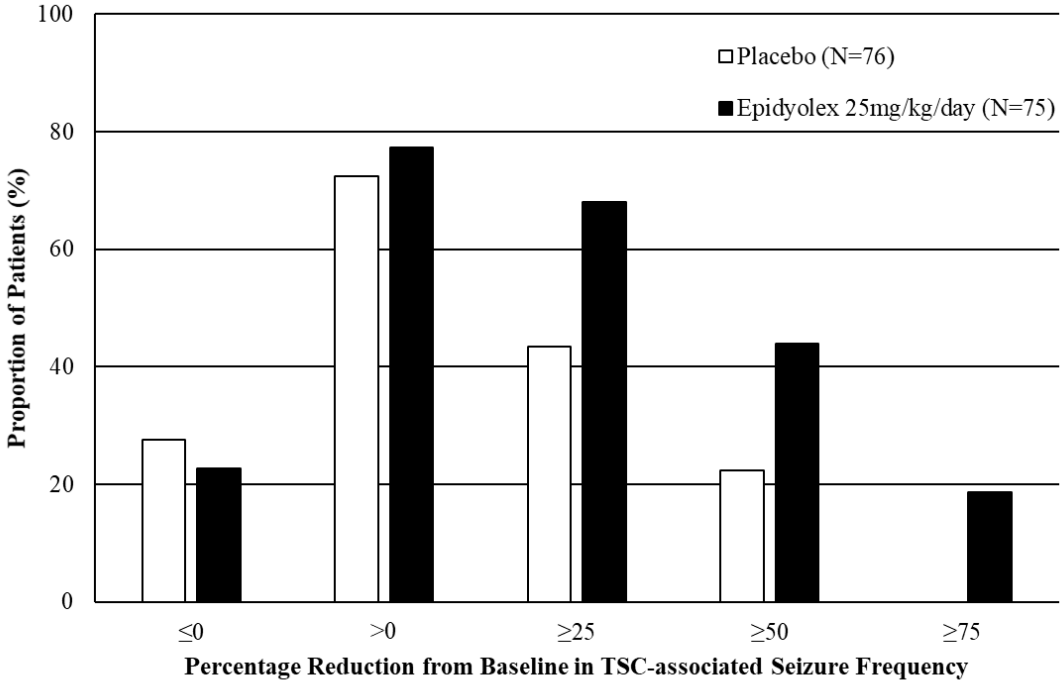
Table 5: **Primary and secondary outcome measures in the TSC study (overall patient population)**

	Study GWPCARE6	
	Epidyolex 25 mg/kg/day (n = 75)	**Placebo** (n = 76)
Primary endpoint – Percentage reduction in TSC-associated seizure frequency [a]		
TSC-associated seizures **% Reduction from Baseline**	48.6%	26.5%
Percent Reduction Compared with Placebo	30.1%	
95% CI	13.9%, 43.3%	

P-value	0.0009	
Key Secondary endpoints		
Percentage of patients with a ≥ 50% reduction P-value [b]	36% 0.0692	22.4%
Total seizures **% Reduction from Baseline** ***Percent Reduction Compared with Placebo*** 95% CI P-value	48.1% 29.1% 12.7%, 42.4% 0.0013	26.9%
Mean S/CGIC results (last visit) P-value	3.0 (sl. improved) 0.027	3.5 (no change)

CI=95% confidence interval.
a=Data for study GWPCARE6 are presented as percent reduction from baseline estimated from a negative binomial regression analysis.
b=The overall p-value is based on a Cochran Mantel Haenszel test.

Figure 3: Cumulative Proportion of Patients by Category of Seizure Response in the Treatment Period for Epidyolex and Placebo in Patients with Tuberous Sclerosis Complex (GWPCARE6)



Compared with placebo, Epidyolex was associated with an increase in the number of TSC-associated seizure free days during the treatment period, equivalent to 2.82 days per 28 days.

The effect of Epidyolex on infantile/epileptic spasms associated with TSC has not been fully assessed.

Open label data

Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was 61% during Week 1–12 (N=199), which was maintained through to Week 37–48, with a median percentage reduction from baseline in TSC-associated seizure frequency of 68%.

Treatment with Clobazam

Based on the results of exploratory subgroup analyses there may be additive anticonvulsant effects of Epidyolex in the presence of clobazam, associated with an increased risk of somnolence and sedation, pneumonia, and hepatocellular injury (see sections 4.4 and 4.5 and 4..8).

The concomitant use of Epidyolex and clobazam requires individualised clinical assessment and potential dose adjustments of either or both medicines based on efficacy, tolerability, and safety.

Safety and efficacy in paediatric patients

The European Medicines Agency has deferred the obligation to submit the results of studies with Epidyolex in one or more subsets of the paediatric population in treatment of seizures associated with DS, LGS and TSC. See section 4.2 for information on paediatric use.

Further information

Abuse

In an abuse potential study, acute administration of Epidyolex to non-dependent adult recreational drug users at therapeutic and supratherapeutic doses produced small responses on positive subjective measures such as “craving” and “desire to take again”. Compared to dronabinol (synthetic THC) and alprazolam, Epidyolex has low abuse potential.

5.2 Pharmacokinetic properties

Absorption

Cannabidiol appears rapidly in plasma with a time to maximum plasma concentration of 2.5–5 hours at steady state.

Steady-state plasma concentrations are attained within 2-4 days of twice daily dosing based on predose (C_{min}) concentrations. The rapid achievement of steady state is related to the multiphasic elimination profile of the drug in which the terminal elimination represents only a small fraction of the drug’s clearance.

In healthy volunteer studies, co-administration of Epidyolex with a high-fat/high-calorie meal increased the rate and extent of absorption (5-fold increase in C_{max} and 4-fold increase in AUC) and reduced the total variability of exposure compared with the fasted state in healthy volunteers.

Although the effect is slightly smaller for a low-fat/low-calorie meal, the elevation in exposure is still marked (C_{max} by 4-fold, AUC by 3-fold). Furthermore, taking Epidyolex with

bovine milk enhanced exposure by approximately 3-fold for C_{max} and 2.5-fold for AUC. Taking Epidyolex with alcohol also caused enhanced exposure to cannabidiol (C_{max} by 1.9-fold, AUC by 1.6-fold).

Distribution

In vitro, > 94% of cannabidiol and its phase I metabolites were bound to plasma protein. Preferential binding is with human serum albumin.

The apparent volume of distribution after oral dosing was high in healthy volunteers at 20,963 L to 42,849 L and greater than in total body water, suggesting a wide distribution of Epidyolex.

Metabolism

Cannabidiol is extensively metabolised by the liver via CYP450 enzymes and the UGT enzymes. The major CYP450 isoforms responsible for the phase I metabolism of cannabidiol are CYP2C19 and CYP3A4. The UGT isoforms responsible for the phase II conjugation of cannabidiol are UGT1A7, UGT1A9, and UGT2B7.

The phase I metabolites identified in standard in vitro assays were 7-COOH-CBD, 7-OH-CBD, and 6-OH-CBD (a minor circulating metabolite).

After multiple dosing with Epidyolex, the 7-OH-CBD metabolite (active in a preclinical seizure model) circulates in human plasma at lower concentrations than the parent drug cannabidiol (~ 40% of CBD exposure) based on AUC. The circulating metabolite with the highest plasma concentrations is 7-COOH-CBD with steady state exposure around 50-fold higher than CBD. This metabolite probably has no intrinsic activity.

Elimination

The half-life of Epidyolex in plasma was 56–61 hours after twice daily dosing for 7 days in healthy volunteers.

The plasma clearance of cannabidiol following a single 1500 mg dose of cannabidiol is about 1111 L/h.

Linearity/non-linearity

After single fasting dosing, cannabidiol exposure over the range 750–6000 mg increases in a less than dose-proportional manner.

Kinetics in specific patient groups

Hepatic impairment

No effects on cannabidiol or metabolite exposures were observed following administration of a single dose of Epidyolex 200 mg in subjects with mild hepatic impairment.
Subjects with moderate and severe hepatic impairment showed higher plasma concentrations of cannabidiol (approximately 2.5–5.2-fold higher AUC compared to healthy subjects with normal hepatic function).

Renal impairment

No effects on the C_{max} or AUC of cannabidiol were observed following administration of a single dose of Epidyolex 200 mg in subjects with mild, moderate, or severe renal impairment when compared to patients with normal renal function. Patients with end-stage renal disease were not studied.

Children and adolescents

Pharmacokinetics of cannabidiol has not been studied in paediatric patients < 2 years of age. A small number of patients < 2 years old with treatment-resistant epilepsy (including TSC, LGS and DS) have been administered Epidyolex in clinical trials and in an expanded access programme.

5.3 Preclinical safety data

Genotoxicity

Genotoxicity studies have not detected any mutagenic or clastogenic effect.

Carcinogenicity

In a carcinogenicity study in mice, oral administration of Epidyolex (30, 100, or 300 mg/kg/day) for 2 years increased the incidence of benign hepatocellular adenomas at all doses tested in male mice and at the highest dose in female mice. At the highest dose evaluated, plasma exposures (AUC) in mice were approximately 7 times greater than the anticipated exposure in humans at a dosage of 25 mg/kg/day.

A study of the carcinogenic potential of cannabidiol in rats is ongoing.

Reproductive toxicity

No adverse reactions were observed on male or female fertility or reproduction performance in rats at doses of up to 250 mg/kg/day (approximately 34-fold greater than the maximum recommended human dose (MRHD) at 25 mg/kg/day).

An embryo-foetal development (EFD) study performed in rabbits evaluated doses of 50, 80, or 125 mg/kg/day. Decreased foetal body weights and increased foetal structural variations associated with maternal toxicity were observed at a dose of 125 mg/kg/day. Maternal plasma cannabidiol exposures at the no-observed-adverse-effect-level (NOAEL) were less than that in humans at a dosage of 25 mg/kg/day.

In rats the EFD study evaluated doses of 75, 150, or 250 mg/kg/day. Embryofoetal mortality was observed at the high dose, with no treatment-related effects on implantation loss at the low or mid doses. The NOAEL was associated with maternal plasma exposures (AUC) approximately 9 times greater than the anticipated exposure in humans at a dosage of 25 mg/kg/day.

A pre- and post-natal development study was performed in rats at doses of 75, 150, or 250 mg/kg/day. Decreased growth, delayed sexual maturation, behavioural changes (decreased activity), and adverse effects on male reproductive organ development (small testes in adult offspring) and fertility were observed in the offspring at doses

≥ 150 mg/kg/day. The NOAEL was associated with maternal plasma cannabidiol exposures approximately 5 times that in humans at a dosage of 25 mg/kg/day.

Toxicity tests with juvenile animals

In juvenile rats, administration of cannabidiol for 10 weeks (subcutaneous doses of 0 or 15 mg/kg on postnatal days [PNDs] 4–6 followed by oral administration of 0, 100, 150, or 250 mg/kg on PNDs 7–77) resulted in increased body weight, delayed male sexual maturation, neurobehavioural effects, increased bone mineral density, and liver hepatocyte vacuolation.

A no-effect dose was not established. The lowest dose causing developmental toxicity in juvenile rats (15 mg/kg subcutaneous / 100 mg/kg oral) was associated with cannabidiol exposures (AUC) approximately 8 times that in humans at 25 mg/kg/day.

Other data

Non-clinical abuse potential studies showed that cannabidiol does not produce cannabinoid-like behavioural responses, including generalisation of delta-9-tetrahydrocannabinol (THC) in a drug discrimination study. Cannabidiol also does not produce animal self-administration, suggesting it does not produce rewarding effects and does not result in physical dependence or withdrawal syndrome.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each ml of oral solution contains
100 mg cannabidiol.
Contains refined sesame oil, ethanol, Sucralose, and strawberry flavour components (including benzyl alcohol).

6.2 Incompatibilities

Enteral administration: Tubes made of polyvinyl chloride and polyurethane should not be used.

6.3 Shelf life

24 months

Shelf life after opening

Shelf life after first opening: Use within 12 weeks after first opening the bottle.

6.4 Special precautions for storage

Store below 30°C.
Do not freeze.
Keep out of the reach of children.

6.5 Nature and contents of container

Amber glass bottle (type III) with a childproof and tamperproof screw cap (polypropylene). 1 ml oral dosing syringe (graduated in 0.05 ml increments) (plunger HDPE and barrel polypropylene) and bottle adaptor (LDPE).

5 ml oral dosing syringe (graduated in 0.1 ml increments) (plunger HDPE and barrel polypropylene) and bottle adaptor (LDPE).

Each pack contains:
One 100 ml bottle
Two 1 ml oral dosing syringes and one bottle adaptor
Two 5 ml oral dosing syringes and one bottle adaptor

Dispensing category: A

6.6 Special precautions for disposal and other handling

Instructions for handling

Nasogastric tubes made of silicone, with a length of at least 50 cm and no more than 125 cm and a diameter of at least 5 FR and no more than 12 FR, can be used.
Gastric tubes made of silicone, with a length of 0.8 to 4 cm and a diameter of 12 FR to 24 FR, can be used.

After administration, the enteral feeding tube should be flushed at least once with room temperature water. If more than one drug is being administered, the tube should be flushed between each drug. It is recommended that the flushing volume is approximately 5 times the priming volume of the tube. The flushing volume may need to be modified in patients with fluid restrictions.

The manufacturer's specifications should be observed for the maximum period of use of the tubes and the associated syringes.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals Switzerland GmbH Grafenauweg 8 6300 Zug, Switzerland.

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

September 2023