ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Epidyolex 100 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 100 mg cannabidiol.

Excipients with known effect

Each ml of solution contains:

79 mg anhydrous ethanol

736 mg refined sesame oil

0.0003 mg benzyl alcohol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear, colourless to yellow solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epidyolex is indicated for 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.

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

4.2 Posology and method of administration

Epidyolex should be initiated and supervised by physicians with experience in the treatment of epilepsy.

Posology

For LGS and DS

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

The recommended starting dose of cannabidiol is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a 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 dose recommendations for LGS, DS and TSC are summarised in the following table:

Table 1: Dose 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 cannabidiol)
- Two 5 ml syringes graduated in 0.1 ml increments (each 0.1 ml increment corresponds to 10 mg cannabidiol)

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.

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

Discontinuation
If cannabidiol has to be discontinued, the dose should be decreased gradually. 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.

Missed doses
In the case of one or more missed doses, the missed doses should not be compensated. Dosing should be resumed at the existing treatment schedule. In the case of more than 7 days' missed doses, re-titration to the therapeutic dose should be made.

Special populations

Elderly
Clinical trials of cannabidiol 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, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other concurrent therapy (see sections 4.4 under hepatocellular injury and 5.2).

Renal impairment
Cannabidiol 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 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) (see sections 4.3 and 4.4). 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.

Table 2: Dose adjustments in patients with moderate or severe hepatic impairment

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.

Paediatric population

With LGS and DS
There is no relevant use of cannabidiol in children aged below 6 months. The safety and efficacy of cannabidiol in children aged 6 months to 2 years have not yet been established. No data are available.

With TSC
There is no relevant use of cannabidiol in children aged below 1 month. The safety and efficacy of cannabidiol in children aged 1 month to 2 years have not yet been established. Currently available data in patients aged 1 to 2 years are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

Oral use
Food may increase cannabidiol levels and therefore it should be taken consistently either with or without food, including the ketogenic diet. When taken with food, a similar composition of food should be considered, if possible (see section 5.2).

Oral administration is recommended; however, when necessary, nasogastric and gastrostomy tubes may be acceptable methods for enteral administration.

For further information on the use of feeding tubes see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Cannabidiol 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 dose adjustment of clobazam should be considered if transaminase elevations occur.

Resolution of transaminase elevations occurred with discontinuation of cannabidiol or reduction of cannabidiol 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 cannabidiol, without dose reduction.

Patients with baseline transaminase levels above the ULN had higher rates of transaminase elevations when taking cannabidiol. 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 cannabidiol.

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 outcome. 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 cannabidiol treatment.

Prior to starting treatment with cannabidiol, obtain serum transaminases (ALT and AST) and total bilirubin levels.

Routine monitoring
Serum transaminases and total bilirubin levels should be obtained at 1 month, 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.

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 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) (see section 4.5).

Somnolence and sedation

Cannabidiol can cause somnolence and sedation, which occur more commonly early 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.

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, should the benefit-risk be negative. In the phase 3 clinical trials investigating LGS, DS and TSC, the observed frequency of status epilepticus was similar between the cannabidiol and placebo groups.

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 mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for cannabidiol.

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.

Decreased weight

Cannabidiol can cause weight loss or decreased weight gain (see section 4.8). In LGS, DS and TSC patients, this appeared to be dose-related. In some cases, decreased weight was reported as an adverse event. 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.

Excipients with known effect

Sesame oil
This medicinal product contains refined sesame oil which may rarely cause severe allergic reactions.

Benzyl alcohol
This medicinal product contains 0.0003 mg/ml benzyl alcohol corresponding to 0.0026 mg per maximal Epidyolex dose (Epidyolex 12.5 mg/kg per dose (TSC) for an adult weighing 70 kg).
Benzyl alcohol may cause allergic reactions.
High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

Ethanol
Each ml of Epidyolex contains 79 mg of ethanol, equivalent to 10% v/v anhydrous ethanol, i.e., up to 691.3 mg ethanol/ per maximal single Epidyolex dose (12.5 mg/kg) for an adult weighing 70 kg (9.9 mg ethanol/ kg). For an adult weighing 70 kg, this is equivalent to 17 ml of beer, or 7 ml of wine per dose.

Populations not studied

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

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 or CYP2C19 inducers

The strong CYP3A4/2C19 inducing agent rifampicin (600 mg administered once daily) decreased plasma concentrations of cannabidiol and of 7-hydroxy-cannabidiol (7-OH-CBD; an active metabolite of cannabidiol) by approximately 30% and 60%, respectively. Other strong inducers of CYP3A4 and/or CYP2C19, such as carbamazepine, enzalutamide, mitotane, and St. John's wort, when administered concomitantly with cannabidiol, may also cause a decrease in the plasma concentrations of cannabidiol and of 7-OH-CBD by a similar amount. These changes may result in a decrease in 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, therefore, caution should be taken when co-administering medicinal products that are known inhibitors of these UGTs. Dose reduction of cannabidiol and/or the inhibitor may be necessary when given in combination.

Concomitant AED treatments

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.

The potential for drug-drug interactions with other concomitant AEDs has been assessed in healthy volunteers and patients with epilepsy for clobazam, valproate, stiripentol and everolimus.

Clobazam
When cannabidiol and clobazam are 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-OH-CBD, for which plasma area under the curve (AUC) increased by 47% (see section 5.2). 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 (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 cannabidiol.

Valproate
Concomitant use of cannabidiol and valproate increases the incidence of transaminase enzyme elevations (see section 4.8). The mechanism of this interaction remains unknown. 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. 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 cannabidiol and valproate increases the incidence of diarrhoea and events of decreased appetite. 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.

Everolimus
Coadministration of cannabidiol (12.5 mg/kg twice daily) with the P-gp and CYP3A4 substrate everolimus (5 mg) in a healthy volunteer study led to an increase in everolimus exposure of approximately 2.5-fold for both C_{max} and AUC. The mechanism for this interaction is believed to be inhibition of intestinal P-gp efflux, leading to increased bioavailability of everolimus, because cannabidiol did not affect midazolam exposure in another interaction study. The half-life of everolimus was not affected, confirming the lack of systemic inhibitory effects of cannabidiol on P-gp and CYP3A4 activity. When initiating cannabidiol in patients taking everolimus, monitor therapeutic drug levels of everolimus and adjust the dose accordingly. When initiating everolimus in patients taking a stable dose of cannabidiol, a lower starting dose of everolimus is recommended, with therapeutic drug monitoring.

<u>Potential for cannabidiol to affect other medicinal products</u>

Sensitive substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9, and UGT2B7
Sensitive CYP1A2 substrates
In vivo data from steady-state dosing with cannabidiol (750 mg twice daily) when co-administered with a single dose of caffeine (200 mg), a sensitive CYP1A2 substrate, showed increased caffeine exposure by 15% for C_{max} and 95% for AUC compared to when caffeine was administered alone. These data indicate that cannabidiol is a weak inhibitor of CYP1A2. Similar modest increases in exposure may be observed with other sensitive CYP1A2 substrates (e.g., theophylline or tizanidine). The clinical importance of these findings has not been studied. The patient should be closely monitored for adverse drug reactions.

Sensitive CYP2B6 substrates
Coadministration of cannabidiol (7.5 mg/kg twice daily) with a single dose of bupropion (150 mg), a sensitive CYP2B6 substrate, decreased bupropion exposure by 19% for C_{max} and 20% for AUC

(compared to bupropion administered alone), which is within the observed variability and therefore not clinically meaningful. Changes in exposures of CYP2B6 substrates are unknown when concomitantly used with cannabidiol at doses above 7.5 mg/kg twice daily.

Sensitive CYP2C8 substrates
Because of potential inhibition of enzyme activity, dose reduction of substrates of CYP2C8 should be considered, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with cannabidiol.

Sensitive CYP2C9 substrates
Coadministration of cannabidiol (7.5 mg/kg twice daily) with a single dose of tolbutamide (500 mg), (a moderately sensitive CYP2C9 substrate), did not result in changes in plasma concentration of tolbutamide compared to tolbutamide administered alone. Similar C_{max} and AUC of tolbutamide is predicted with steady-state dosing of cannabidiol (12.5 mg/kg twice daily) when coadministered with a single dose of tolbutamide (500 mg), compared to when tolbutamide was administered alone. No dose adjustment is needed for drugs that are substrates of CYP2C9 (e.g. phenytoin) when given concomitantly with cannabidiol.

Sensitive CYP2C19 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.

Sensitive UGT1A9 substrates
Coadministration of cannabidiol (7.5 mg/kg twice daily) with a single dose of mycophenolate mofetil (1500 mg) increased mycophenolic acid (a sensitive UGT1A9 substrate) exposure by 16% for C_{max} and 35% for AUC. An increase in mycophenolic acid exposure by 9% for C_{max} and 58% for AUC is predicted when mycophenolate mofetil (1500 mg) was coadministered with steady-state dosing of cannabidiol (12.5 mg/kg twice daily). Increases in concentration of UGT1A9 substrates may be observed when concomitantly used with cannabidiol. Consider a dose reduction of sensitive UGT1A9 substrates, such as mycophenolic acid, where even minor changes in concentration may lead to serious adverse reactions. Adjust dosing based on clinical judgement.

Sensitive UGT2B7 substrates
Coadministration of cannabidiol (7.5 mg/kg twice daily) with a single dose of zidovudine (300 mg), a sensitive UGT2B7 substrate, increased zidovudine exposure by 7% for C_{max} and 19% for AUC (compared to zidovudine administered alone) which is not expected to be clinically significant. No clinically meaningful changes in plasma exposures of zidovudine are predicted when zidovudine is coadministered with steady-state dosing of cannabidiol (12.5 mg/kg twice daily). No dose adjustment is needed for drugs that are substrates of UGT2B7 (e.g. lamotrigine) when given concomitantly with cannabidiol.

In vitro assessment of interaction with UGT enzymes
The metabolite 7-carboxy-cannabidiol (7-COOH-CBD) is 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.

Sensitive P-gp substrates given orally
Coadministration of cannabidiol with orally administered everolimus, a P-gp and CYP3A4 substrate, has increased everolimus bioavailability likely due to inhibition of intestinal P-gp efflux of everolimus. Increases in exposure of other orally administered sensitive P-gp substrates (e.g., sirolimus, tacrolimus, or digoxin) may occur on coadministration with cannabidiol. Therapeutic drug monitoring and dose reduction of other P-gp substrates should be considered when given orally and concurrently with cannabidiol.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

As a precautionary measure, cannabidiol should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

Breast-feeding

There are no clinical data on the presence of cannabidiol 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).

There are no human studies on excretion of cannabidiol in breast milk. Given that cannabidiol is highly protein bound and will likely pass freely from plasma into milk, as a precaution, breast-feeding should be discontinued during treatment.

Fertility

No human data on the effect of cannabidiol on 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

Cannabidiol 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 cannabidiol in the recommended dose range of 10 to 25 mg/kg/day are shown below.

The most common adverse reactions are somnolence (23%), decreased appetite (21%), diarrhoea (20%), pyrexia (16%), vomiting (12%) and fatigue (10%).

The most frequent causes of discontinuation were transaminase elevation (2%), somnolence (2%) and decreased appetite (1%).

Tabulated list of adverse reactions

Adverse reactions reported with cannabidiol in placebo-controlled clinical studies are listed in the table 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.

Table 3: Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reactions from clinical trials
Infections and infestations	Common	Pneumonia[a]
		Urinary tract infection
Blood and lymphatic system disorders	Very common	Haemoglobin decreased
		Haematocrit decreased
Metabolism and nutrition disorders	Very common	Decreased appetite
Psychiatric disorders	Common	Irritability
		Aggression
Nervous system disorders	Very common	Somnolence[a]
	Common	Lethargy
		Seizure
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very common	Diarrhoea
		Vomiting
	Common	Nausea
Hepatobiliary disorders	Common	AST increased
		ALT increased
		GGT increased
Skin and subcutaneous tissue disorders	Common	Rash
Renal and urinary disorders	Common	Blood creatinine increased
General disorders and administration site conditions	Very common	Pyrexia
		Fatigue
Investigations	Common	Weight decreased

[a] Grouped Terms: **Pneumonia:** Pneumonia, Pneumonia RSV, Pneumonia mycoplasmal, Pneumonia adenoviral, Pneumonia viral, Aspiration pneumonia; **Somnolence:** Somnolence, Sedation.

Description of selected adverse reactions

Hepatocellular injury
Cannabidiol can cause dose-related elevations of ALT and AST (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 cannabidiol-treated patients compared with < 1% in patients on placebo.

Less than 1% of cannabidiol-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 cannabidiol.

Risk factors for hepatocellular injury
Concomitant valproate and clobazam, dose of cannabidiol and baseline transaminase elevations

Concomitant valproate and clobazam
In cannabidiol-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 medicinal product.

Dose
ALT elevations greater than 3 times the ULN were reported in 15% of patients taking cannabidiol 20 or 25 mg/kg/day compared with 3% in patients taking cannabidiol 10 mg/kg/day.

The risk of ALT elevations was higher at doses 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 cannabidiol 20 or 25 mg/kg/day, the frequency of treatment-emergent 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 cannabidiol 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 (see section 4.4) with cannabidiol in LGS, DS and TSC, including 29% of cannabidiol-treated patients (30% of patients taking cannabidiol 20 or 25 mg/kg/day and 27% of patients taking cannabidiol 10 mg/kg/day). These adverse reactions were observed at higher incidences at doses 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 cannabidiol-treated patients taking clobazam, compared with 14% in cannabidiol-treated patients not on clobazam).

Seizures
In the controlled trial in TSC patients, an increased frequency of adverse events associated with seizure worsening was seen at doses above 25 mg/kg/day. Although no clear pattern was established, the adverse events reflected increased seizure frequency or intensity, or new seizure types. The frequency of adverse events associated with seizure worsening was 11% for patients taking 25 mg/kg/day cannabidiol and 18% for patients taking cannabidiol doses greater than 25 mg/kg/day, compared to 9% in patients taking placebo.

Decreased weight
Cannabidiol can cause weight loss or decreased weight gain (see section 4.4). In LGS, DS and TSC patients, the decrease in weight appeared to be dose-related, with 21% of patients on cannabidiol 20 or 25 mg/kg/day experiencing a decrease in weight of ≥ 5%, compared to 7% in patients on cannabidiol 10 mg/kg/day. In some cases, the decreased weight was reported as an adverse event (see Table 3 above). Decreased appetite and weight loss may result in slightly reduced height gain.

Diarrhoea
Cannabidiol can cause dose-related diarrhoea. In controlled trials in LGS and DS, the frequency of diarrhoea was 13% in patients receiving 10 mg/kg/day cannabidiol and 21% in patients receiving 20 mg/kg/day cannabidiol, compared to 10% in patients receiving placebo. In a controlled trial in TSC, the frequency of diarrhoea was 31% in patients receiving 25 mg/kg/day cannabidiol and 56% in patients receiving doses greater than 25 mg/kg/day cannabidiol, compared to 25% in patients receiving placebo.

In the clinical trials, the first onset of diarrhoea was typically in the first 6 weeks of treatment with cannabidiol. The median duration of diarrhoea was 8 days. The diarrhoea led to cannabidiol dose reduction in 10% of patients, temporary dose interruption in 1% of patients and permanent discontinuation in 2% of patients.

Haematologic abnormalities
Cannabidiol 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 cannabidiol-treated patients receiving 10, 20, or 25 mg/kg/day. A corresponding decrease in haematocrit was also observed, with a mean change of −1.3% in cannabidiol-treated patients.

Twenty-seven percent (27%) of cannabidiol-treated patients with LGS and DS and 38% of cannabidiol-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).

Increases in creatinine
Cannabidiol 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 cannabidiol. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS, DS or TSC.

Pneumonia
Pneumonia events have been observed in controlled trials with cannabidiol in patients with LGS, DS, or TSC, including 6% of cannabidiol-treated patients compared with 1% of patients receiving placebo.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. listed in Appendix V.

4.9 Overdose

Symptoms

Experience with doses higher than the recommended therapeutic dose is limited. Mild diarrhoea and somnolence have been reported in healthy adult subjects taking a single dose of 6 000 mg; this equates to a dose of over 85 mg/kg for a 70 kg adult. These adverse reactions resolved upon study completion.

Management of overdose

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

Pharmacotherapeutic group: antiepileptics, other antiepileptics; 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 1 (TRPV-1) channels, as well as modulation of adenosine-mediated signalling through inhibition of adenosine cellular uptake via the equilibrative nucleoside transporter 1 (ENT-1).

Pharmacodynamic effects

In patients, there is a potential additive anticonvulsant effect from the bi-directional pharmacokinetic interaction between cannabidiol and clobazam, which leads to increases in circulating levels of their respective active metabolites, 7-OH-CBD (approximately 1.5-fold) and N-CLB (approximately 3-fold) (see sections 4.5, 5.1 and 5.2).

Clinical efficacy

Adjunctive therapy in patients with Lennox-Gastaut syndrome (LGS)
The efficacy of cannabidiol 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. Approximately 50% of the patients were taking concomitant clobazam. Of the patients that were not taking clobazam, the majority had previously taken and subsequently discontinued clobazam treatment.

The primary endpoint was the percentage change from baseline in drop seizures per 28 days over the treatment period for the cannabidiol group compared to placebo. Drop seizures were defined as atonic, tonic, or tonic-clonic seizures that led or could have led to a fall or injury. Key secondary endpoints were the proportion of patients with at least a 50% reduction in drop seizure frequency, the percentage change from baseline in total seizure frequency, and Subject/Caregiver Global Impression of Change at the last visit.

Subgroup analyses were conducted on multiple factors, including cAEDs. Results of the subgroup analysis of patients treated with clobazam compared to patients treated without clobazam, indicated that there is residual statistical uncertainty regarding the treatment effect of cannabidiol in patients not taking clobazam. In this population, efficacy has not been established.

Table 4 summarises the primary endpoint of percent reduction from baseline in drop seizures, and the key secondary measure of proportion of patients with at least a 50% reduction in drop seizure frequency, as well as results of the subgroup analysis for these outcome measures in patients treated with concomitant clobazam.

Table 4: Primary and ≥ 50% responder key secondary outcome measures and subgroup analysis in LGS studies

		Overall	**N**	**Subgroup with clobazam**	**N**
DROP SEIZURES PER 28 DAYS					
Percentage reduction from baseline[a]					
GWPCARE3	Placebo	17.2%	76	22.7%	37
	10 mg/kg/day	37.2%	73	45.6%	37
	20 mg/kg/day	41.9%	76	64.3%	36
GWPCARE4	Placebo	21.8%	85	30.7%	42
	20 mg/kg/day	43.9%	86	62.4%	42
Difference or percent reduction compared with placebo (95% CI), p-value[b]					
GWPCARE3	10 mg/kg/day	19.2 (7.7, 31.2) p = 0.0016		29.6% (2.4%, 49.2%) p = 0.0355[c]	
	20 mg/kg/day	21.6 (6.7, 34.8) p = 0.0047		53.8% (35.7%, 66.8%) p< 0.0001[c]	
GWPCARE4	20 mg/kg/day	17.2 (4.1, 30.3) p = 0.0135		45.7% (27.0%, 59.6%) p< 0.0001[c]	
⩾ 50% REDUCTION IN DROP SEIZURES (RESPONDER ANALYSIS)					
Percentage of ⩾ 50% responders, p-value[d]					

GWPCARE3	Placebo	14.5%	76	21.6%	37
	10 mg/kg/day	35.6%	73	40.5%	37
		p = 0.0030		p = 0.0584[c]	
	20 mg/kg/day	39.5%	76	55.6%	36
		p = 0.0006		p = 0.0021[c]	
GWPCARE4	Placebo	23.5%	85	28.6%	42
	20 mg/kg/day	44.2%	86	54.8%	42
		p = 0.0043		p = 0.0140[c]	

CI=95% confidence interval.
[a] Data for the overall population are presented as median percent reduction from baseline. Data for the with clobazam subgroup are presented as percent reduction from baseline estimated from a negative binomial regression analysis.
[b] Overall data are presented as estimated median difference and p-value from a Wilcoxon rank-sum test. Data for the with clobazam subgroup are estimated from a negative binomial regression analysis.
[c] Nominal p-value.
[d] The Overall p-value is based on a Cochran-Mantel-Haenszel test; the nominal p-values for the with clobazam subgroup are based on logistic regression analysis.

Additional secondary outcome measures in the subgroup of patients treated with concomitant clobazam
Cannabidiol was associated with an increase in the percentage of subjects experiencing a greater than or equal to 75% reduction in drop seizure frequency during the treatment period in each trial (11% 10 mg/kg/day cannabidiol, 31% to 36% 20 mg/kg/day cannabidiol, 3% to 7% placebo).

In each trial, patients receiving cannabidiol experienced a greater median percentage reduction in total seizures compared with placebo (53% 10 mg/kg/day, 64% to 66% 20 mg/kg/day, 25% for each placebo group; p = 0.0025 for 10 mg/kg/day and p< 0.0001 for each 20 mg/kg/day group vs. placebo).

Greater improvements in overall condition, as measured by Global Impression of Change scores at the last visit, were reported by caregivers and patients with both doses of cannabidiol (76% on 10 mg/kg/day, 80% for each group on 20 mg/kg/day, 31% to 46% on placebo; p = 0.0005 for 10 mg/kg/day and p< 0.0001 and 0.0003 for 20 mg/kg/day vs. placebo).

Compared with placebo, cannabidiol was associated with an increase in the number of drop seizure-free days during the treatment period in each trial, equivalent to 3.3 days per 28 days (10 mg/kg/day) and 5.5 to 7.6 days per 28 days (20 mg/kg/day).

Adjunctive therapy in patients with Dravet syndrome
The efficacy of cannabidiol 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. Approximately 65% of the patients were taking concomitant clobazam. Of the patients that were not taking clobazam, the majority had previously taken and subsequently discontinued clobazam treatment.

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 percentage change from baseline in convulsive seizures per 28 days over the treatment period (GWPCARE1) for the cannabidiol groups compared to placebo. Convulsive seizures were defined as atonic, tonic, clonic, and tonic-clonic seizures. Key secondary endpoints for GWPCARE2 were the proportion of patients with at least a 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 a 50% reduction in convulsive seizure frequency.

Subgroup analyses were conducted on multiple factors, including cAEDs. Results of the subgroup analysis of patients treated with clobazam compared to patients treated without clobazam, indicated that there is residual statistical uncertainty regarding the treatment effect of cannabidiol in patients not taking clobazam. In this population, efficacy has not been established.

Table 5 summarises the primary endpoint of percent reduction from baseline in convulsive seizures, and the key secondary measure of proportion of patients with at least a 50% reduction in convulsive seizure frequency, as well as results of the subgroup analysis for these outcome measures in patients treated with concomitant clobazam.

Table 5: Primary and ≥ 50% responder key secondary outcome measures and subgroup analysis in DS studies

		Overall	N	Subgroup with clobazam	N
CONVULSIVE SEIZURES PER 28 DAYS					
Percentage reduction from baseline[a]					
GWPCARE2	Placebo	26.9%	65	37.6%	41
	10 mg/kg/day	48.7%	66	60.9%	45
	20 mg/kg/day	45.7%	67	56.8%	40
GWPCARE1	Placebo	13.3%	59	18.9%	38
	20 mg/kg/day	38.9%	61	53.6%	40
Difference or percent reduction compared with placebo (95% CI), p-value[b]					
GWPCARE2	10 mg/kg/day	29.8% (8.4%, 46.2%) p = 0.0095		37.4% (13.9%, 54.5%) p = 0.0042[c]	
	20 mg/kg/day	25.7% (2.9%, 43.2%) p = 0.0299		30.8% (3.6%, 50.4%) p = 0.0297[c]	
GWPCARE1	20 mg/kg/day	22.8 (5.4, 41.1) p = 0.0123		42.8% (17.4%, 60.4%) p = 0.0032[c]	
⩾ 50% REDUCTION IN CONVULSIVE SEIZURES (RESPONDER ANALYSIS)					
Percentage of ⩾ 50% responders, p-value[d]					
GWPCARE2	Placebo	26.2%	65	36.6%	41
	10 mg/kg/day	43.9% p = 0.0332	66	55.6% p = 0.0623[c]	45
	20 mg/kg/day	49.3% p = 0.0069	67	62.5% p = 0.0130[c]	40
GWPCARE1	Placebo	27.1%	59	23.7%	38
	20 mg/kg/day	42.6% p = 0.0784	61	47.5% p = 0.0382[c]	40

CI=95% confidence interval.

[a] For study GWPCARE1, overall data are presented as median percent reduction from baseline. Data for study GWPCARE2 and the with clobazam subgroup are presented as percent reduction from baseline estimated from a negative binomial regression analysis.

[b] For study GWPCARE1, overall data are presented as estimated median difference and p-value from a Wilcoxon rank-sum test. Data for study GWPCARE2 and the with clobazam subgroup are estimated from a negative binomial regression analysis.

[c] Nominal p-value.

[d] The Overall p-value is based on a Cochran-Mantel-Haenszel test; the nominal p-value for the with clobazam subgroup is based on logistic regression analysis.

Additional secondary outcome measures in the subgroup of patients treated with concomitant clobazam
Cannabidiol was associated with an increase in the percentage of subjects experiencing a greater than or equal to 75% reduction in convulsive seizure frequency during the treatment period in each trial (36% 10 mg/kg/day cannabidiol, 25% for each 20 mg/kg/day cannabidiol group, 10% to 13% placebo).

In each trial, patients receiving cannabidiol experienced a greater percentage reduction in total seizures compared with placebo (66% 10 mg/kg/day, 54% to 58% 20 mg/kg/day, 27% to 41% placebo; p = 0.0003 for 10 mg/kg/day and p = 0.0341 and 0.0211 for 20 mg/kg/day vs. placebo).

Greater improvements in overall condition, as measured by Global Impression of Change scores at the last visit, were reported by caregivers and patients with both doses of cannabidiol (73% on 10 mg/kg/day, 62% to 77% on 20 mg/kg/day, 30% to 41% on placebo; p = 0.0009 for 10 mg/kg/day and p = 0.0018 and 0.0136 for 20 mg/kg/day vs. placebo).

Compared with placebo, cannabidiol was associated with an increase in the number of convulsive seizure-free days during the treatment period in each trial, equivalent to 2.7 days per 28 days (10 mg/kg/day) and 1.3 to 2.2 days per 28 days (20 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, cannabidiol 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 (N = 366) who completed the studies were enrolled into the long-term open-label extension (OLE) study (GWPCARE5). In the subgroup of LGS patients treated with concomitant clobazam for 37 to 48 weeks (N = 168), the median percentage reduction from baseline in drop seizure frequency was 71% during Week 1-12 (N = 168), which was maintained through to Week 37-48, with a median percentage reduction from baseline in drop seizure frequency of 62%.

Across both randomised DS studies, 97.7% of patients (N = 315) who completed the studies were enrolled into GWPCARE5. In the subgroup of DS patients treated with concomitant clobazam for 37 to 48 weeks (N = 148), the median percentage reduction from baseline in convulsive seizure frequency was 64% during Week 1-12 (N = 148, which was maintained through to Week 37-48, with a median percentage reduction from baseline in convulsive seizure frequency of 58%.

Adjunctive therapy in patients with tuberous sclerosis complex (TSC)
The efficacy of cannabidiol (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 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 cannabidiol 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.

Cannabidiol 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 6 summarises the primary endpoint of percent reduction from baseline in TSC-associated seizures, and the key secondary measure of proportion of patients with at least a 50% reduction in TSC-associated seizure frequency for the maximum recommended dose of 25 mg/kg/day.

Table 6: Primary and ≥ 50% responder key secondary outcome measures in the TSC study (overall patient population)

	Study GWPCARE6	
	Cannabidiol 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 endpoint - ≥ 50% REDUCTION IN TSC-associated seizures (RESPONDER ANALYSIS)		
Percentage of patients with a ≥ 50% reduction	36%	22.4%
P-value[b]	0.0692	

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.

Subgroup analyses with and without clobazam treatment

In the GWPCARE6 study, 22.7% of TSC patients in the 25 mg/kg/day group and 32.9% in the placebo group were taking concomitant clobazam. Results of subgroup analysis by clobazam use showed additive anticonvulsant effects of cannabidiol in the presence of clobazam.

In the subgroup of patients treated with concomitant clobazam, patients receiving cannabidiol 25 mg/kg/day experienced a 61.1% reduction from baseline in TSC-associated seizure frequency compared to a 27.1% reduction in the placebo group, based on a negative binomial regression analysis. Compared with placebo, cannabidiol was associated with a 46.6% reduction (nominal p = 0.0025) in TSC-associated seizures (95% CI: 20.0%, 64.4%).

In the subgroup of patients treated without concomitant clobazam, patients receiving cannabidiol 25 mg/kg/day experienced a 44.4 % reduction from baseline in TSC-associated seizure frequency compared to a 26.2% reduction in the placebo group; based on a negative binomial regression analysis. Compared with placebo, cannabidiol was associated with a 24.7% reduction (nominal p = 0.0242) in TSC-associated seizures (95% CI: 3.7%, 41.1%).

Additional secondary outcome measures for cannabidiol 25 mg/kg/day (overall patient population)

Cannabidiol was associated with an increase in the percentage of subjects (16.0%) experiencing a greater than or equal to 75% reduction in TSC-associated seizure frequency during the treatment period compared with the placebo group (0%).

Patients receiving cannabidiol experienced a greater percentage reduction in total seizures (48.1%) compared with placebo (26.9%).

Global Impression of Change scores at the last visit were reported by caregivers and patients. 68.6% of patients in the cannabidiol group vs. 39.5% in the placebo group experienced an improvement.

Compared with placebo, cannabidiol 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 cannabidiol 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. The median modal dose was 25 mg/kg/day and median treatment period was 90 weeks (range: 2.6-209 weeks). In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was 54% during Week 1–12 (N = 199), which was maintained through to Week 85–96 (N = 98), with a median percentage reduction from baseline in TSC-associated seizure frequency of 75%.

Abuse

In a human abuse potential study, acute administration of cannabidiol to non-dependent adult recreational drug users at therapeutic and supratherapeutic doses produced small responses on positive subjective measures such as Drug Liking and Take Drug Again. Compared to dronabinol (synthetic THC) and alprazolam, cannabidiol has low abuse potential.

Paediatric population

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

The GWPCARE6 study, conducted in patients with TSC, included 8 children between 1 and 2 years of age across all treatment groups. Although data are limited, the observed treatment effect and tolerability were similar to that seen in patients 2 years of age and older, however, efficacy, safety and pharmacokinetics in children < 2 years of age have not been established (see section 4.2).

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 pre-dose (C_{trough}) 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 cannabidiol (750 or 1 500 mg) 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 cannabidiol with bovine milk enhanced exposure by approximately 3-fold for C_{max} and 2.5-fold for AUC. Taking cannabidiol with alcohol also caused enhanced exposure to cannabidiol, with a 63% greater AUC.

In the randomised controlled trials, the timing of dose of cannabidiol with respect to meal times was not restricted. In patients, a high fat meal was also shown to increase the bioavailability of cannabidiol (3-fold). This increase was moderate when the prandial state was not fully known, i.e., 2.2-fold increase of the relative bioavailability.

To minimise the variability in the bioavailability of cannabidiol in the individual patient, administration of cannabidiol should be standardised in relation to food intake including a ketogenic diet (high-fat meal) i.e., Epidyolex should be taken consistently with or without food. When taken with food, a similar composition of food should be considered, if possible.

Distribution

In vitro, > 94% of cannabidiol and its phase I metabolites were bound to plasma proteins, with preferential binding to 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 total body water, suggesting a wide distribution of cannabidiol.

Biotransformation and elimination

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

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.

Studies in healthy subjects showed there were no major differences in the plasma exposure to cannabidiol in CYP2C19 intermediate and ultra-rapid metabolisers when compared to extensive metabolisers.

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 cannabidiol, the 7-OH-CBD metabolite (active in a preclinical model of seizure) circulates in human plasma at lower concentrations than the parent drug cannabidiol (~ 40% of CBD exposure) based on AUC.

Excretion
The plasma clearance of cannabidiol following a single 1 500 mg dose of cannabidiol is about 1 111 L/h. Cannabidiol is predominantly cleared by metabolism in the liver and gut and excreted in faeces, with renal clearance of parent drug being a minor pathway.

Cannabidiol does not interact with the major renal and hepatic transporters in a way that is likely to result in relevant drug-drug interactions.

Linearity

The C_{max} and AUC of cannabidiol are close to dose-proportional over the therapeutic dose range (10-25 mg/kg/day). After single dosing, exposure over the range 750-6 000 mg increases in a less than dose-proportional manner, indicating that absorption of cannabidiol may be saturable. Multiple dosing in TSC patients also indicated that absorption is saturable at doses above 25 mg/kg/day.

Pharmacokinetics in special patient groups

Effect of age, weight, sex, race
Population pharmacokinetic analyses demonstrated that there were no clinically relevant effects of age, body weight, sex, or race on exposure to cannabidiol.

Elderly
Pharmacokinetics of cannabidiol have not been studied in subjects > 74 years of age.

Paediatric patients
Pharmacokinetics of cannabidiol have not been studied in paediatric patients < 2 years of age.

A small number of patients < 2 years with treatment-resistant epilepsy (including LGS, DS and TSC) have been exposed to cannabidiol in clinical trials and in an expanded access programme.

Renal impairment
No effects on the C_{max} or AUC of cannabidiol were observed following administration of a single dose of cannabidiol 200 mg in subjects with mild (CLcr 50 to 80 ml/min), moderate (CLcr 30 to < 50 ml/min), or severe (CLcr < 30 ml/min) renal impairment when compared to patients with normal renal function (CLcr > 80 ml/min). Patients with end-stage renal disease were not studied.

Hepatic impairment
No effects on cannabidiol or metabolite exposures were observed following administration of a single dose of cannabidiol 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). Cannabidiol should be used with caution in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment. The dose titration should be performed as detailed in section 4.2.

Pharmacokinetic/pharmacodynamic relationship(s)

In LGS

In patients with LGS, population pharmacokinetic pharmacodynamic (PK/PD) modelling indicated the presence of an exposure efficacy relationship for the likelihood of achieving a ≥ 50% reduction in drop seizure frequency across the cannabidiol dose range tested (0 [placebo], 10 and 20 mg/kg/day). There was a significant positive correlation between the derived AUC of cannabidiol and the probability of a ≥ 50% response. The responder rate analysis also showed a correlation in the exposure–response relationship for the active metabolite of cannabidiol (7-OH-CBD). PK/PD analysis also demonstrated that systemic exposures to cannabidiol were correlated with some adverse events, namely elevated

ALT, AST, diarrhoea, fatigue, GGT, loss of appetite, rash, and somnolence (see section 4.8). Clobazam (separate analysis) was a significant covariate which caused the probability of GGT to increase, loss of appetite to decrease, and somnolence to increase.

In TSC

In TSC patients there is no exposure-response relationship based on efficacy endpoints, as the doses evaluated are at the high end of the dose-response relationship. However, an exposure-response relationship was determined for the 7-OH-CBD metabolite in relation to AST elevation. No other PK/PD relationships with safety endpoints were identified for CBD or its metabolites.

Drug interaction studies

In vitro assessment of drug interactions
Cannabidiol is a substrate for CYP3A4, CYP2C19, UGT1A7, UGT1A9 and UGT2B7. Cannabidiol has the potential to inhibit CYP2B6, CYP2C8, CYP2C19 and to induce CYP2B6 at clinically relevant concentrations.

The metabolite 7-COOH-CBD is an inhibitor of UGT1A1, UGT1A4 and UGT1A6-mediated activity, *in vitro* at clinically relevant concentrations (see section 4.5).

Cannabidiol and the metabolite 7-OH-CBD do not interact with the major renal or hepatic uptake transporters and therefore are unlikely to result in relevant drug-drug interactions: 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. *In vitro*, cannabidiol and 7-OH-CBD are not substrates for or inhibitors of efflux transports P-gp/MDR1, BCRP or BSEP. *In vivo* data with everolimus show that cannabidiol can affect P-gp-mediated efflux of a P-gp substrate in the intestine (see section 4.5) but cannabidiol did not inhibit or induce CYP3A4 based on an *in vivo* midazolam study. The metabolite 7-COOH-CBD is a P-gp/MDR1 substrate and has the potential to inhibit BCRP, OATP1B3, and OAT3.

In vivo assessment of drug interactions
Drug interaction studies with AEDs
Potential interactions between cannabidiol (750 mg twice daily in healthy volunteers and 20 mg/kg/day in patients) and other AEDs were investigated in drug-drug interaction studies in healthy volunteers and in patients and in a population pharmacokinetic analysis of plasma drug concentrations from placebo-controlled studies in the treatment of patients with LGS.

The combination of cannabidiol with clobazam caused an elevation in exposure to the active metabolite N-desmethylclobazam, with no effect on clobazam levels. Although exposure to cannabidiol was not notably affected by clobazam use, the levels of an active metabolite, 7-OH-CBD, were elevated by this combination. Therefore, dose adjustments of cannabidiol or clobazam may be required.

Coadministration of cannabidiol and everolimus led to an increase in everolimus exposure. Therefore, dose adjustments and therapeutic drug monitoring of everolimus may be required when everolimus and cannabidiol are concomitantly used.

The *in vivo* interactions for clobazam, everolimus and other concomitant AEDs are summarised in the table below.

Table 7: Drug interactions between cannabidiol and concomitant antiepileptic drugs

Concomitant AED	Influence of AED on cannabidiol	Influence of cannabidiol on AED
Clobazam	No effect on cannabidiol levels. Interaction resulting in an increase in exposure of the active metabolite 7-OH-CBD in HV* studies. [a]	No effect on clobazam levels. Interaction resulting in approximately 3-fold increase in N-desmethylclobazam metabolite exposure. [b]
Valproate	No effect on CBD or its metabolites.	No effect on valproic acid exposure or exposure to the putative hepatotoxic metabolite 2-propyl-4-pentenoic acid (4-ene-VPA).
Stiripentol	No effect on cannabidiol levels. Interaction resulting in a decrease (approximately 30%) in C_{max} and AUC of the active metabolite 7-OH-CBD in trials conducted in HV* and patients with epilepsy.	Interaction resulting in an approximate 28% increase in C_{max} and 55% increase in AUC in a HV* study and increases of 17% in C_{max} and 30% increases in AUC in patients.
Everolimus	The effect of everolimus on cannabidiol has not been assessed.	Coadministration of cannabidiol (12.5 mg/kg twice daily) with everolimus (5 mg) resulting in an approximate 2.5-fold increase in everolimus exposure for both C_{max} and AUC in a HV* study.

[a] average increases of 47% in AUC and 73% in C_{max}.
[b] based on C_{max} and AUC.
*HV = Healthy Volunteer.

5.3 Preclinical safety data

Mutagenicity and carcinogenicity

In a carcinogenicity study in mice, oral administration of cannabidiol (0 [water], 0 [vehicle], 30, 100, or 300 mg/kg/day) for 2 years increased the incidence of benign hepatocellular adenomas in male mice at all doses tested and in female mice at the highest dose tested. At the highest dose evaluated, plasma cannabidiol exposures (AUC) in mice were approximately 3 times greater than the anticipated exposure in humans at the maximum recommended human dose (MRHD) of 25 mg/kg/day.

In a 104-week carcinogenicity study in rats, oral administration of cannabidiol (0 [water], 0 [vehicle], 15, 50, and 150 mg/kg/day) increased the incidences of focal Leydig cell hyperplasia and Leydig cell adenoma across all male dose levels. At the lowest dose evaluated, plasma cannabidiol exposures (AUC) were less than 1-fold the clinical plasma exposure at the MRHD. One Leydig cell carcinoma occurred in a male at the highest dose evaluated, corresponding to an exposure level 10-fold the clinical plasma exposure at the MRHD. Leydig cell tumours in rats are generally considered of limited relevance to humans.

Genotoxicity studies have not detected any mutagenic or clastogenic activity of cannabidiol or major human metabolites.

Reproductive toxicity

Cannabidiol: No adverse reactions were observed on male or female fertility or reproduction performance in rats at doses up to 250 mg/kg/day (approximately 14-fold greater than the MRHD of 25 mg/kg/day).

Cannabidiol: The embryofoetal development (EFD) study performed in rabbits evaluated doses of 50, 80, or 125 mg/kg/day. The dose level of 125 mg/kg/day induced decreased foetal body weights and increased foetal structural variations associated with maternal toxicity. Maternal plasma cannabidiol

exposures at the no-observed-adverse-effect-level (NOAEL) for embryofoetal developmental toxicity in rabbits were less than that in humans at the MRHD of 25 mg/kg/day.

Cannabidiol: 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 cannabidiol exposures (AUC) approximately 13 times greater than the anticipated exposure in humans at the MRHD of 25 mg/kg/day.

7-COOH-CBD: In rats, an EFD study evaluated doses of 25, 50 and 100 mg/kg/day 7-COOH-CBD. Embryofoetal malformations and variations were observed at the highest dose tested. There were no other drug-related maternal or developmental effects. The highest no-effect dose for embryofoetal toxicity in rats was associated with maternal plasma 7-COOH-CBD exposures (AUC) approximately 4 times greater than the anticipated exposure in humans at the MRHD of 25 mg/kg/day.

Cannabidiol: 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 7 times that in humans at the MRHD of 25 mg/kg/day.

7-COOH-CBD: A pre- and post-natal development study was performed in rats at doses of 20, 40 or 75 mg/kg/day 7-COOH-CBD. Administration of these doses was well tolerated, and no adverse effects were observed on maternal animals or subsequent offspring until adulthood. The no-effect dose for pre- and post-natal developmental toxicity in rats was associated with maternal plasma 7-COOH-CBD exposures approximately 7 times that in humans at the MRHD of 25 mg/kg/day.

Juvenile toxicity

Cannabidiol: In juvenile rats, administration of cannabidiol for 10 weeks (subcutaneous doses of 0 or 15 mg/kg on post-natal 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 4 times that in humans at the MRHD of 25 mg/kg/day.

In another study, cannabidiol was dosed to juvenile rats from PNDs 4-21 (as a subcutaneous injection) and from PNDs 22-50 (as an intravenous injection). A NOAEL of 15 mg/kg/day was established.

7-COOH-CBD: In juvenile rats, subcutaneous administration of the metabolite 7-COOH-CBD (0, 20, 40, or 80 mg/kg/day) on PNDs 4-6 followed by oral gavage on PNDs 7-77, for a total of 10 weeks, resulted in mortality, ophthalmic abnormalities, and accelerated female sexual maturation at ≥40 mg/kg/day, and long-term neurobehavioural (increased locomotor activity, decreased auditory startle response habituation and prepulse inhibition, delayed maze learning) and reproductive functional impairment (disrupted estrous cyclicity, decreased sperm concentration and increased abnormal sperm; decreased mating, fertility, and fecundity indices; increased preimplantation loss), decreased brain weight, and decreased bone density at 80 mg/kg/day. The no-effect dose was established at 20 mg/kg/day, associated with 7-COOH-CBD exposures (AUC) approximately equivalent to those in humans at the MRHD of 25 mg/kg/day cannabidiol.

Abuse

Animal abuse-related studies show that cannabidiol does not produce cannabinoid-like behavioural responses, including generalisation to delta-9-tetrahydrocannabinol (THC) in a drug discrimination

study. Cannabidiol also does not produce animal self-administration, suggesting it does not produce rewarding effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refined sesame oil
Anhydrous ethanol
Sucralose (E955)
Strawberry flavour (including benzyl alcohol)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Use within 12 weeks after first opening the bottle.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottle (type III) with a child-resistant and tamper-evident screw cap (polypropylene).

The following pack sizes are available for Epidyolex 100 mg/ml oral solution:

100 ml (1 × 100 ml bottle) with 2 × 5 ml and 2 × 1 ml calibrated oral dosing syringes (HDPE plunger and Polypropylene barrel) and two bottle adaptors (LDPE).

300 ml (3 × 100 ml bottles) with 2 × 5 ml and 2 × 1 ml calibrated oral dosing syringes (HDPE plunger and Polypropylene barrel) and three bottle adaptors (LDPE).

The 5 ml syringes are graduated in 0.1 ml increments and the 1 ml syringes are graduated in 0.05 ml increments.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Nasogastric tubes made of silicone, with a length of more than 50 cm and maximum of 125 cm and a diameter of more than 5 FR and maximum of 12 FR, can be used. Nasogastric tubes made of silicone, being 50 cm or shorter and 5 FR or less in diameter should be avoided. 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. Tubes made of polyvinyl chloride and polyurethane should not be used.

After administration, the enteral feeding tube should be flushed at least once with room temperature water. If more than one medicinal product is being administered, the tube should be flushed between each medicinal product. It is recommended that the flushing volume is approximately 5 times the priming volume of the tube (with a minimum of 3 ml for the shortest/narrowest tubes to a maximum of

20 ml for the longest/largest tubes). The flushing volume may need to be modified in patients with fluid restrictions.

Enteral tubes with ENFit® connections require the use of ENFit compatible syringes and bottle adaptors. To maximise dose accuracy, 1 ml syringes should be used for doses ≤ 1 ml.

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

7. MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals Ireland Ltd
5th Floor
Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1389/001
EU/1/19/1389/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2019
Date of latest renewal: 26 July 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency, https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Jazz Pharmaceuticals Netherlands B.V.,
Stationsplein 13A, 3818 LE, Amersfoort
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Oral solution - Carton containing 100 ml (1 x 100 ml bottle) oral solution

1. NAME OF THE MEDICINAL PRODUCT

Epidyolex 100 mg/ml oral solution
cannabidiol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 100 mg cannabidiol.

3. LIST OF EXCIPIENTS

Contains refined sesame oil, ethanol and strawberry flavour components (including benzyl alcohol).

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
One 100 ml bottle
Two 1 ml oral syringes with bottle adaptor
Two 5 ml oral syringes with bottle adaptor

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Discard unused portion 12 weeks after first opening.
Date of first opening:

____/_____/_____

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals Ireland Ltd
5th Floor
Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1389/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

epidyolex

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Oral solution - Carton containing 300 ml (3 x 100 ml bottles) oral solution

1. NAME OF THE MEDICINAL PRODUCT

Epidyolex 100 mg/ml oral solution
cannabidiol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 100 mg cannabidiol.

3. LIST OF EXCIPIENTS

Contains refined sesame oil, ethanol and strawberry flavour components (including benzyl alcohol).

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
3 × 100 ml bottles
Two 1 ml oral syringes with bottle adaptor
Two 5 ml oral syringes with two bottle adaptors

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Discard unused portion 12 weeks after first opening.
Date of first opening:

____/_____/_____

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals Ireland Ltd
5th Floor
Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1389/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

epidyolex

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Epidyolex 100 mg/ml oral solution
cannabidiol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 100 mg cannabidiol.

3. LIST OF EXCIPIENTS

Contains refined sesame oil, ethanol and strawberry flavour components (including benzyl alcohol).

4. PHARMACEUTICAL FORM AND CONTENTS

100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard unused portion 12 weeks after first opening
Date of first opening:
____/_____/_____

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals Ireland Ltd
5th Floor
Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1389/001 (1 × 100 ml bottle pack)
EU/1/19/1389/002 (3 × 100 ml bottles pack)

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Epidyolex 100 mg/ml oral solution
cannabidiol

Read all of this leaflet carefully before you or the patient start taking this medicine because it contains important information for you or the patient

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Epidyolex is and what it is used for
2. What you or the patient need to know before taking Epidyolex
3. How you or the patient should take Epidyolex
4. Possible side effects
5. How to store Epidyolex
6. Contents of the pack and other information

1. What Epidyolex is and what it is used for

Epidyolex contains cannabidiol, a medicine which can be used to treat epilepsy, a condition where someone has seizures or fits.

Epidyolex is used in combination with clobazam or with clobazam and other antiepileptic medicines to treat seizures that occur with two rare conditions, called Dravet syndrome and Lennox-Gastaut syndrome. It can be used in adults, adolescents and children of at least 2 years of age.

Epidyolex is also used in combination with other antiepileptic medicines to treat seizures that occur with a genetic disorder called tuberous sclerosis complex (TSC). It can be used in adults, adolescents and children of at least 2 years of age.

2. What you or the patient need to know before taking Epidyolex

Do not take Epidyolex
- if you are allergic to cannabidiol or any of the other ingredients of this medicine (listed in section 6).
- if your doctor determines that you have certain abnormal liver blood tests.

Warnings and precautions
Talk to your doctor or pharmacist before taking Epidyolex or during treatment if:
- you have or have had liver problems, as your doctor may need to change the dose of Epidyolex or may decide that Epidyolex is not appropriate for you.
  Your doctor may do blood tests to check your liver before you start taking this medicine and during treatment, as Epidyolex can cause liver problems. If your liver is not working properly, your treatment may need to be stopped.
- you notice unusual changes in your mood or behaviour or have thoughts of harming or killing yourself. **Contact your doctor or go to a hospital straight away** (see section 4).

- Epidyolex can make you feel sleepy. Do not drive, operate machinery, or take part in activities that require you to be alert and have fine control, such as cycling, until you know how Epidyolex affects you.
- you stop taking Epidyolex suddenly (see section 3).
- your seizures happen more often, or if you experience a severe seizure while taking Epidyolex. **Contact your doctor or go to a hospital straight away.**
- you experience weight loss or are unable to gain weight. Your doctor will monitor your weight and will evaluate if Epidyolex treatment should be continued.

Children and adolescents
Epidyolex is not recommended for use in children under the age of 2 years.

Other medicines and Epidyolex
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Taking Epidyolex with certain other medicines may cause side effects, affect how the other medicines work, or affect how Epidyolex works. Do not start or stop other medicines without talking to your doctor or pharmacist.
Tell your doctor if you are taking any of the following medicines, as your dose may need to be adjusted:
- other epilepsy medicines, such as carbamazepine, clobazam, lorazepam, stiripentol and valproate, that are used to treat seizures
- other medicines used to treat TSC, including everolimus or tacrolimus
- medicines used to treat acid reflux (heartburn or acid regurgitation) such as omeprazole
- mitotane (a medicine used to treat tumours in the adrenal gland)
- morphine or diflunisal (medicines used to treat pain)
- efavirenz (a medicine used to treat HIV/AIDS)
- theophylline (a medicine used to treat asthma)
- caffeine (a medicine for babies who need help breathing)
- propofol (an anaesthetic used for people undergoing surgery)
- simvastatin, fenofibrate, gemfibrozil, (medicines used to reduce cholesterol/lipids)
- enzalutamide (a medicine to treat prostate cancer)
- St. John's wort (*Hypericum perforatum*) (a herbal medicine used to treat mild anxiety)
- medicines to treat bacterial infections, such as rifampin, clarithromycin and erythromycin

Epidyolex with food
Always take Epidyolex according to your doctor's instructions and consistently either with or without food, including high-fat meals (such as ketogenic diet). If you take Epidyolex with food, a similar meal type (e.g., similar fat content) should be taken if possible. (See also section 3, How to take Epidyolex).

Pregnancy, breast-feeding and fertility
If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not take Epidyolex while you are pregnant unless the doctor decides the benefits outweigh the potential risks.
You should not breast-feed whilst taking Epidyolex, as Epidyolex is likely to be present in breast milk.

Driving and using machines
Talk to your doctor about driving, using machines or when children undertake activities such as cycling or other sports, because you may feel sleepy after taking this medicine.
You should not drive, use machines or take part in activities that require you to be alert and have fine control, until it is established that your ability to perform such activities is not affected.

Epidyolex contains sesame oil, alcohol (ethanol), strawberry flavour components (including benzyl alcohol).
Epidyolex contains refined sesame oil which may rarely cause severe allergic reactions.

Each ml of Epidyolex contains 79 mg of ethanol equivalent to 10% v/v anhydrous ethanol, i.e., up to 691.3 mg ethanol per maximal single Epidyolex dose (12.5 mg/kg) for an adult weighing 70 kg (9.9 mg ethanol/kg). For an adult weighing 70 kg, this is equivalent to 17 millilitres (ml) of beer, or 7 ml of wine per dose. The small amount of alcohol in this medicine will not have any noticeable effects.

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

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).

Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).

3. How you or the patient should take Epidyolex

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Epidyolex is an oral solution (a liquid to be swallowed). Your doctor and pharmacist will tell you how much (number of ml) Epidyolex to take each day, how many times a day you should take it and which syringe you should use for your dose (1 ml or 5 ml).

Your doctor will calculate the dose according to your body weight. You may start on a low dose that your doctor gradually increases over time. Contact your doctor if you are unsure of your dose or if you think your dose may need to be changed.

Taking Epidyolex with food can increase the amount of medicine your body takes in. You should try, as far as possible, to take Epidyolex consistently either with or without food, and according to your daily routine, so you get the same effect each time. If you take Epidyolex with food, a similar meal type (e.g., similar fat content) should be taken if possible.

If necessary, Epidyolex may be taken via a nasogastric or gastrostomy tube. Your doctor will give you directions how to do so. Check with your doctor or pharmacist if you are not sure.

Tell your doctor if you have liver problems because the doctor may need to adjust the dose.

Do not reduce the dose or stop this medicine unless the doctor tells you to.

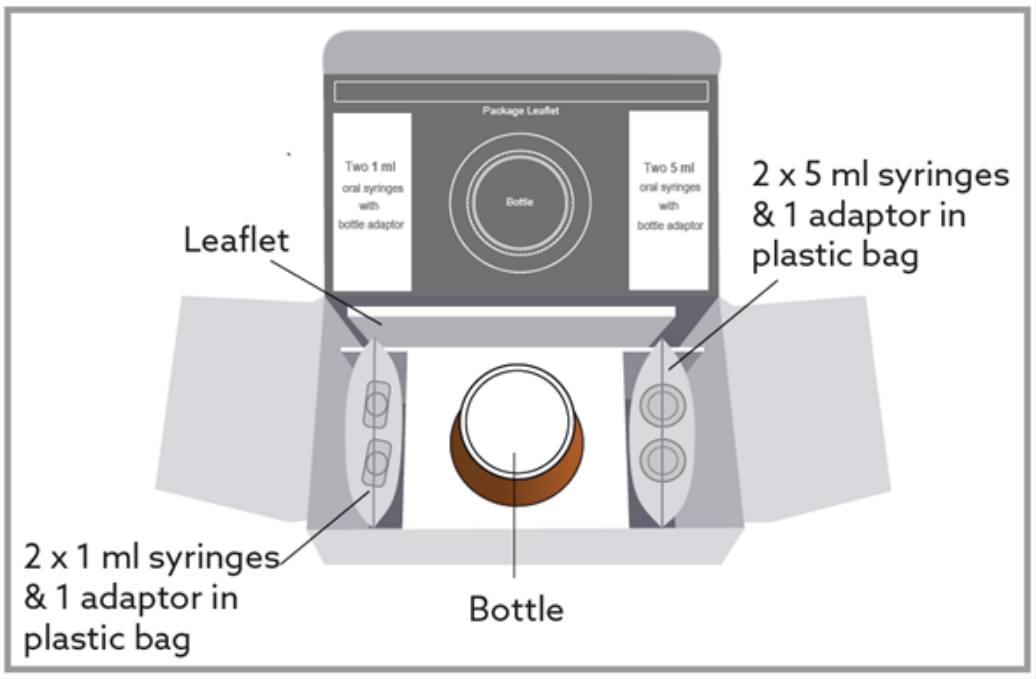
<u>Instructions for the oral use of Epidyolex</u>

The 1-bottle pack contains the following items:
- Epidyolex oral solution bottle
- a plastic bag containing two 1 ml oral syringes and a bottle adaptor
- a plastic bag containing two 5 ml oral syringes and a bottle adaptor

The 3-bottle pack contains the following items:
- three Epidyolex oral solution bottles
- a plastic bag containing two 1 ml oral syringes and a bottle adaptor

- a plastic bag containing two 5 ml oral syringes and two bottle adaptors

A spare syringe of each size is provided in the pack in case the first one is damaged or lost. For the 3-bottle pack, all three adaptors from both syringe packs are required.



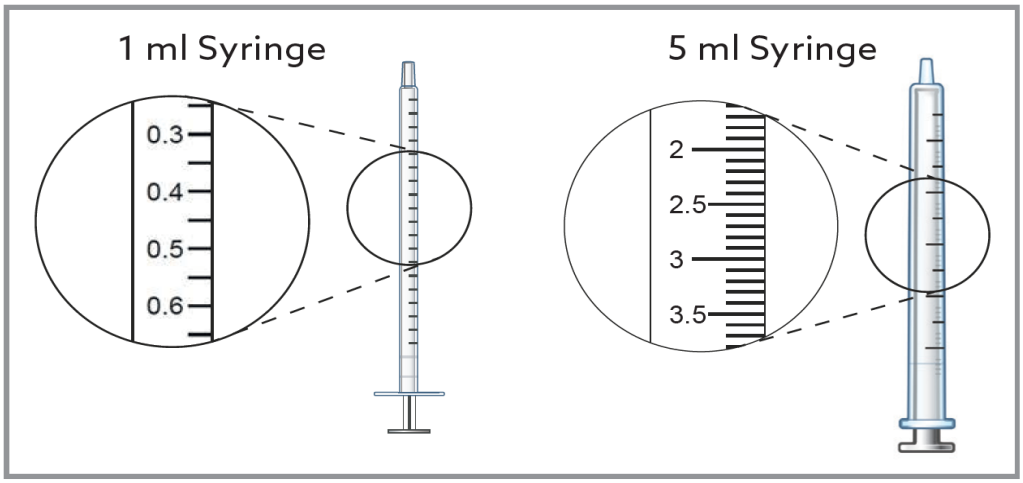
The above picture is for illustration purposes only.

1. Open the bag containing the correct oral syringe to measure your dose.

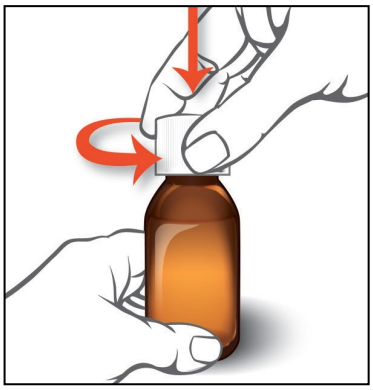
   - If your dose is **1 ml (100 mg) or less**, you should use the smaller 1 ml syringe.
   - If your dose is **more than 1 ml (100 mg)**, you should use the larger 5 ml syringe.

   - If your dose is **more than 5 ml (500 mg)**, you will need to use the larger 5 ml syringe more than once. In this case, keep careful track of how many times you have filled the syringe (e.g., by marking off each 5 ml dose, respectively) so that you take the right dose.

It is important that you use the correct oral syringe to measure your dose. Your doctor or pharmacist will let you know which syringe to use depending on the dose that has been prescribed.
Following the directions from the doctor or pharmacist, the bag containing the other syringes and adaptor should be discarded from the pack unless your doctor or pharmacist tells you to keep both syringes until your final dose has been reached. If you are prescribed a 3-bottle pack all three adaptors should be retained.

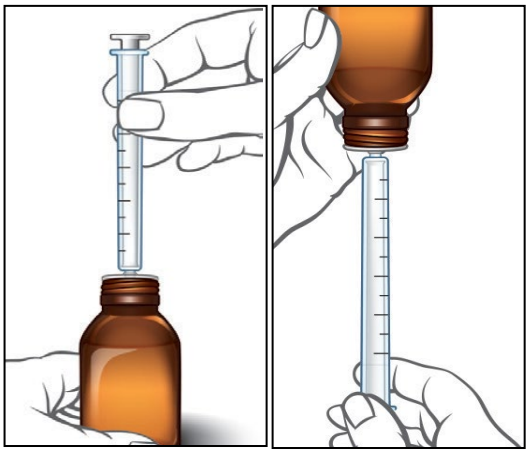


2. Remove the child-resistant cap on the bottle by pushing the cap down whilst turning the cap anti-clockwise.



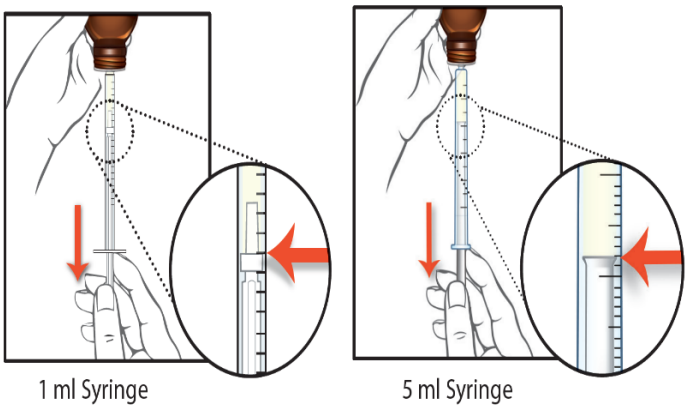
3. Push the bottle adaptor firmly into the neck of the bottle, and make sure it is fully inserted. The adaptor could come off and cause choking if it is not fully inserted.

4. Insert the tip of the correct oral syringe fully into the bottle adaptor, and with the oral syringe in place, turn the bottle upside down.

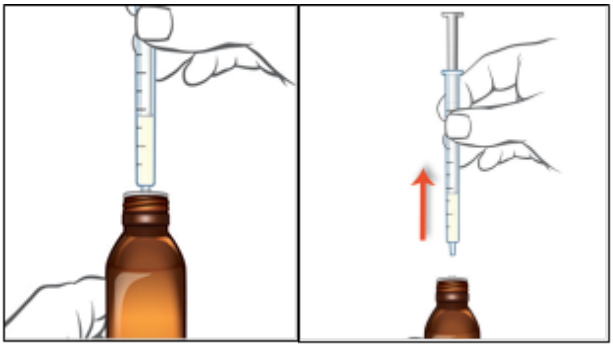


5. Slowly pull back the plunger of the syringe, so the volume (number of ml) of solution needed is drawn into the syringe. Line up the end of the plunger with the prescribed volume marking required, as shown opposite.

   If there is an air bubble in the syringe, push the liquid back into the bottle whilst keeping the bottle upside down, and repeat Step 5 until the bubble has gone.

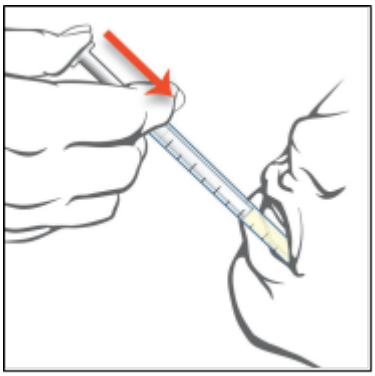


6. Turn the bottle the right side up, and carefully remove the oral syringe from the adaptor.



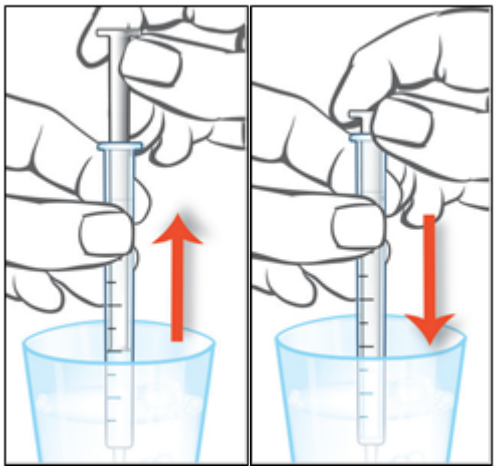
7. Place the tip of the oral syringe inside the cheek, and gently push the plunger to release the medicine. Do not push the plunger forcefully or direct the medicine to the back of the mouth or throat.

   If the dose is more than 5 ml, repeat Steps 4 to 7 to give the remaining dose using the 5 ml oral syringe.



8. Screw the child-resistant cap back on the bottle tightly, by turning the cap clockwise – you do not need to remove the bottle adaptor, as the cap will fit over it.

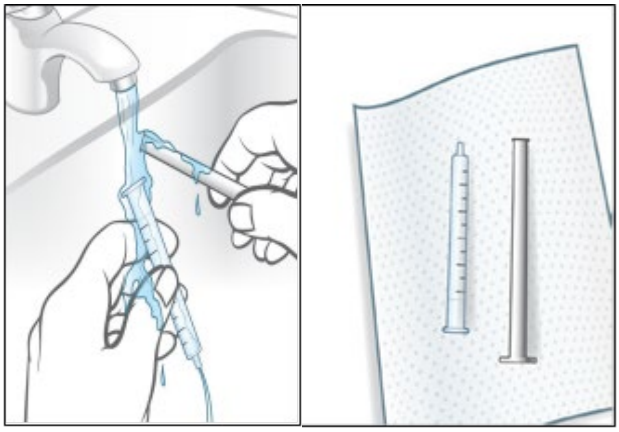
9. Fill a cup with warm soapy water and clean the oral syringe by drawing water in and out using the plunger.



10. Remove the plunger from the barrel of the syringe, and rinse both parts under tap water. Do not place the oral syringe in a dishwasher.

    Shake off any water from both parts and allow them to dry in the air until the next use. Make sure the oral syringe is completely dry before the next use, or it could make the solution appear cloudy if water gets in the bottle.

    If the solution in the bottle has turned cloudy, this doesn't change how well it works. Continue to use the medicine as normal.



If you or your patient take more Epidyolex than you should
If you may have taken more Epidyolex than you should, tell a doctor or pharmacist immediately, or contact your nearest hospital casualty department, and take the medicine with you.
Signs of taking more Epidyolex than you should include diarrhoea and sleepiness.
If you or your patient forget to take Epidyolex
If you forget to take a dose, do not take a double dose to make up for a forgotten dose. Take the next dose at your regular time. If you miss many doses, please talk to your doctor about the correct dose to take.
If you or your patient stop taking Epidyolex
Do not reduce the dose or stop taking Epidyolex without first talking to your doctor. Stopping this treatment abruptly could increase your seizures. The doctor will explain how to gradually stop taking Epidyolex.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects could be **very serious**:

Common side effects (may affect more than 1 in 100 people):

- High liver enzymes (transaminases elevations) seen in blood tests, which can be a sign of liver injury, have been reported in patients receiving Epidyolex.

Side effects where the frequency is not known (frequency cannot be estimated from the available data):

- People taking this medicine can have thoughts of harming or killing themselves. If you have these thoughts at any time, contact your doctor.

You may get the following side effects with this medicine. Tell the doctor if you have any of the following:

Very common side effects (may affect more than 1 in 10 people):

- feeling drowsy or sleepy
- diarrhoea
- decreased appetite
- fever
- vomiting
- feeling tired

Common side effects (may affect more than 1 in 100 people):

- seizures
- feeling bad-tempered (irritable, aggressive)
- rash
- lack of energy
- cough
- pneumonia
- weight loss
- feeling sick
- urinary tract infection

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Epidyolex

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date shown on the bottle. The expiry date refers to the last day of that month.

If you have any solution left in the bottle more than 12 weeks after it was first opened, you should not use it.

This medicine does not require any special storage conditions.

Do not throw away any medicine in the wastewater or household waste. Ask your pharmacist about how to throw away any medicine that you no longer use. This will help protect the environment.

6. Contents of the pack and other information

What Epidyolex contains
- The active substance is cannabidiol. Each ml of oral solution contains 100 mg of cannabidiol.
- The other ingredients are refined sesame oil, anhydrous ethanol, sucralose and strawberry flavour (including benzyl alcohol) (see section 2).

What Epidyolex looks like and contents of the pack
Epidyolex is a clear, colourless to yellow oral solution. It comes in an amber glass bottle which has a child-resistant screw cap.

The following pack sizes are available for Epidyolex:

100 ml (1 × 100 ml bottle) with 2 × 5 ml and 2 × 1 ml calibrated oral dosing syringes and two bottle adaptors.

300 ml (3 × 100 ml bottles) with 2 × 5 ml and 2 × 1 ml calibrated oral dosing syringes and three bottle adaptors.

The 5 ml syringes are graduated in 0.1 ml and the 1 ml in 0.05 ml increments.

Not all pack sizes may be marketed.

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This leaflet was last revised in .

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.