

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.

4.2 Posology and method of administration

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

Posology

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).

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.

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 (see section 4.4). 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 (65 years of age and above)

The safety and efficacy of cannabidiol in patients ≥ 65 years of age have not been established.

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). 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 1: Dose adjustments in patients with moderate or severe hepatic impairment

Hepatic Impairment	Starting Dose	Maintenance Dose	Maximum Recommended Dose
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)
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)*

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

Paediatric population

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.

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).

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 (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance, to sesame oil, 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 causes 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, 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.

Ethanol in the formulation

Each ml of Epidyolex contains 79 mg of ethanol. The maximum recommended single dose of Epidyolex (10 mg/kg) will increase the concentration of ethanol in the body by about 13 mg/l. For an adult weighing 70 kg, this is equivalent to 14 millilitres (ml) of beer, or 6 ml of wine per dose.

Effects of alcohol in children less than 6 years old may include sleepiness, behavioural changes, and impaired ability to concentrate and participate in school activities.

The alcohol content should be taken into account in pregnancy and high-risk groups such as patients with liver disease.

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 or CYP2C19 inducers

The strong CYP3A4/2C9 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, 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 drugs 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 and stiripentol. Although no formal drug-drug interaction studies have been performed for other AEDs, phenytoin and lamotrigine are addressed based on *in vitro* data.

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-desmethyloclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition. 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 4.4). 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 (see section 4.4). Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic medicinal products and cannabidiol (see section 4.4).

Concomitant use of 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.

Phenytoin

Exposure to phenytoin may be increased when it is co-administered with cannabidiol, as phenytoin is largely metabolised via CYP2C9, which is inhibited by cannabidiol *in vitro*. There have not been any clinical studies formally investigating this interaction. Phenytoin has a narrow therapeutic index, so combining cannabidiol with phenytoin should be initiated with caution and if tolerability issues arise, dose reduction of phenytoin should be considered.

Lamotrigine

Lamotrigine is a substrate for UGT enzymes including UGT2B7 which is inhibited by cannabidiol *in vitro*. There have not been any clinical studies formally investigating this interaction. Lamotrigine levels may be elevated when it is co-administered with cannabidiol.

Potential for cannabidiol to affect other medicinal products

CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9, and UGT2B7 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.

In vitro data predict drug-drug interactions with CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5' diphospho-glucuronosyltransferase 1A9 (UGT1A9) (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 (e.g., gemfibrozil, morphine, lorazepam) when co-administered with cannabidiol. Co-administration of cannabidiol is also predicted to cause clinically significant interactions with CYP2C8 (repaglinide) and CYP2C9 (e.g., warfarin) substrates.

In vitro data have demonstrated that cannabidiol inhibits CYP2C19, which may cause increased plasma concentrations of medicines that are metabolised by this isoenzyme such as clobazam and omeprazole. Dose reduction should be considered for concomitant medicinal products that are sensitive CYP2C19 substrates or that have a narrow therapeutic index.

Because of potential inhibition of enzyme activity, dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, and CYP2C9 should be considered, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with cannabidiol. Because of potential for both induction and inhibition of enzyme activity, dose adjustment of substrates of CYP1A2 and CYP2B6 should be considered, as clinically appropriate.

In vitro assessment of interaction with UGT enzymes

In vitro data suggest that cannabidiol is a reversible inhibitor of UGT1A9 and UGT2B7-mediated activity at clinically relevant concentrations. The metabolite 7-carboxy-cannabidiol (7-COOH-CBD) is also an inhibitor of UGT1A1, UGT1A4 and UGT1A6-mediated activity *in vitro*. Dose reduction of the substrates may be necessary when cannabidiol is administered concomitantly with substrates of these UGTs.

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

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

The most frequent cause of discontinuations was transaminase elevation.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reactions from clinical trials
Infections and infestations	Common	Pneumonia ^a , Bronchitis, Nasopharyngitis, Urinary tract infection
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Increased appetite
Psychiatric disorders	Common	Irritability, Insomnia, Aggression, Abnormal behaviour, Agitation
Nervous system disorders	Very common	Somnolence ^a
	Common	Lethargy, Drooling, Tremor
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very common	Diarrhoea, Vomiting
Hepatobiliary disorders	Common	AST increased, ALT increased, GGT increased, Liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Rash
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 causes dose-related elevations of ALT and AST (see section 4.4).

In controlled studies for LGS and DS, the incidence of ALT elevations above 3 times the ULN was 13% 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 were 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, the incidence of ALT elevations greater than 3 times the ULN was 23% in patients taking both concomitant valproate and clobazam, 17% in patients taking concomitant valproate (without clobazam), 3% in patients taking concomitant clobazam (without valproate), and 2% in patients taking neither drug.

Dose

ALT elevations greater than 3 times the ULN were reported in 16% of patients taking cannabidiol 20 mg/kg/day compared with 3% in patients taking cannabidiol 10 mg/kg/day.

Baseline transaminase elevations

In controlled trials (see section 5.1) in patients taking cannabidiol 20 mg/kg/day, the frequency of treatment-emergent ALT elevations greater than 3 times the ULN was 31% (84% 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. Five percent (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 events have been observed in controlled trials with cannabidiol in LGS and DS. The frequency in patients receiving 10 mg/kg/day cannabidiol and taking clobazam was 36%. The frequency in patients receiving 20 mg/kg/day cannabidiol and taking clobazam was 41%.

Decreased weight

Cannabidiol can cause weight loss. In LGS and DS patients, the decrease in weight appeared to be dose-related, with 19% of patients on cannabidiol 20 mg/kg/day experiencing a decrease in weight $\geq 5\%$, compared to 8% in patients on cannabidiol 10 mg/kg/day. In some cases, the decreased weight was reported as an adverse event (see the table above). Decreased appetite and weight loss may result in slightly reduced height gain. Continuous weight loss/absence of weight gain should be periodically checked to evaluate if cannabidiol treatment should be continued.

Haematologic abnormalities

Cannabidiol can cause decreases in haemoglobin and haematocrit. In LGS and DS patients, the mean decrease in haemoglobin from baseline to end of treatment was -0.37 g/dL in cannabidiol-treated patients. A corresponding decrease in haematocrit was also observed, with a mean change of -1.4% in cannabidiol-treated patients.

Twenty-seven percent (27%) of cannabidiol-treated patients 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 been determined. In controlled studies in healthy adults and in patients with LGS and DS, 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 and DS.

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 to moderate diarrhoea and somnolence have been reported in healthy adult subjects taking a single dose of 6000 mg; this equates to a dose of over 85 mg/kg for a 70 kg adult. These adverse reactions resolved upon study completion.

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 3 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 3: Primary and $\geq 50\%$ 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	
$\geq 50\%$ REDUCTION IN DROP SEIZURES (RESPONDER ANALYSIS)					
Percentage of $\geq 50\%$ Responders, p-value^d					
GWPCARE3	Placebo	14.5%	76	21.6%	37
	10 mg/kg/day	35.6% p=0.0030	73	40.5% p=0.0584 ^c	37
	20 mg/kg/day	39.5% p=0.0006	76	55.6% p=0.0021 ^c	36
GWPCARE4	Placebo	23.5%	85	28.6%	42
	20 mg/kg/day	44.2% p=0.0043	86	54.8% p=0.0140 ^c	42

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 4 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 4: Primary and $\geq 50\%$ 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	
$\geq 50\%$ REDUCTION IN CONVULSIVE SEIZURES (RESPONDER ANALYSIS)					
Percentage of $\geq 50\%$ 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 who completed the studies were enrolled into the long-term open-label extension study (GWPCARE5). In the subgroup of LGS patients treated with concomitant clobazam for 37 to 48 weeks ($N=161$), the median percentage reduction from baseline in drop seizure frequency was 71% during Week 1-12, which was maintained through to Week 37-48, with a median percentage reduction from baseline in drop seizure frequency of 63%.

Across both randomised DS studies, 97.7% of patients who completed the studies were enrolled into GWPCARE5. In the subgroup of DS patients treated with concomitant clobazam for 37 to 48 weeks ($N=54$), the median percentage reduction from baseline in convulsive seizure frequency was 60% during Week 1-12, which was maintained through to Week 37-48, with a median percentage reduction from baseline in convulsive seizure frequency of 45%.

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 DS and LGS. (See section 4.2 for information on paediatric use).

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.

Co-administration of cannabidiol (750 or 1500 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. 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).

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 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 1500 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. After single dosing, exposure over the range 750-6000 mg increases in a less than dose-proportional manner, indicating that absorption of cannabidiol may be saturable.

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 patients

Pharmacokinetics of cannabidiol have not been studied in patients > 55 years of age.

Paediatric patients

Pharmacokinetics of cannabidiol has not been studied in paediatric patients < 2 years of age. A small number of patients < 2 years with treatment-resistant epilepsy have been exposed to cannabidiol 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, moderate, or severe renal impairment when compared to patients with normal renal function. 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 patients with LGS, population pharmacokinetic pharmacodynamic (PK/PD) modelling indicated the presence of an exposure efficacy relationship for the likelihood of achieving a $\geq 50\%$ 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 $\geq 50\%$ 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.

Drug interaction studies

In vitro assessment of drug interactions

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

In vitro data suggest that cannabidiol is an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9 and UGT2B7-mediated activity at clinically relevant concentrations. The metabolite 7-carboxy-cannabidiol (7-COOH-CBD) is an inhibitor of UGT1A1, UGT1A4 and UGT1A6-mediated activity, *in vitro* at clinically relevant concentrations (see also section 4.5).

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

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

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. Cannabidiol and 7-OH-CBD are not substrates for or inhibitors of efflux transports P-gp/MDR1, BCRP or BSEP at clinically relevant plasma concentrations. 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-desmethyloclobazam. 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. The interactions are summarised in the table below.

Table 5: 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-desmethyloclobazam 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.

^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

Genotoxicity studies have not detected any mutagenic or clastogenic activity.

Reproductive toxicity

No adverse reactions were observed on male or female fertility or reproduction performance in rats at doses up to 250 mg/kg/day (approximately 60-fold greater than the maximum recommended human dose (MRHD) at 20 mg/kg/day).

The embryo-foetal 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 20 mg/kg/day.

In rats, the EFD study evaluated doses of 75, 150, or 250 mg/kg/day. Embryofoetal mortality was observed at the high dose, with no treatment-related effects on implantation loss at the low or mid doses. The NOAEL was associated with maternal plasma exposures (AUC) approximately 50 times greater than the anticipated exposure in humans at 20 mg/kg/day.

A pre- and post-natal development study was performed in rats at doses of 75, 150, or 250 mg/kg/day. Decreased growth, delayed sexual maturation, behavioural changes (decreased activity), and adverse

effects on male reproductive organ development (small testes in adult offspring) and fertility were observed in the offspring at doses ≥ 150 mg/kg/day. The NOAEL was associated with maternal plasma cannabidiol exposures approximately 9 times that in humans at 20 mg/kg/day.

Juvenile toxicity

In juvenile rats, administration of cannabidiol for 10 weeks (subcutaneous doses of 0 or 15 mg/kg on postnatal days [PNDs] 4-6 followed by oral administration of 0, 100, 150, or 250 mg/kg on PNDs 7-77 resulted in increased body weight, delayed male sexual maturation, neurobehavioural effects, increased bone mineral density, and liver hepatocyte vacuolation. A no-effect dose was not established. The lowest dose causing developmental toxicity in juvenile rats (15 mg/kg subcutaneous/100 mg/kg oral) was associated with C_{max} cannabidiol exposures approximately 20 times that in paediatric subjects at 20 mg/kg/day. In another study, cannabidiol was dosed to juvenile rats from PND 4-21 (as a subcutaneous injection) and from PND 22-50 (as an intravenous injection). A NOAEL of 15 mg/kg/day was established.

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 8 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 bottle is packaged in a carton with two 5 ml and two 1 ml calibrated oral dosing syringes (plunger HDPE and barrel polypropylene) and two bottle adapters (LDPE). The 5 ml syringes are graduated in 0.1 ml increments and the 1 ml syringes are graduated in 0.05 ml increments.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

GW Pharma (International) B.V.,
Databankweg 26
3821AL Amersfoort,
The Netherlands
E-mail: info@gwpharm.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1389/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency, <http://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

GW Pharma (International) B.V., Databankweg 26
3821AL Amersfoort, The Netherlands

GW Pharma Limited,
Kent Science Park, Sittingbourne, Kent, ME9 8AG, United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

OUTER CARTON

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 8 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

GW Pharma (International) B.V., Databankweg 26
3821AL Amersfoort, The Netherlands

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 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 8 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

GW Pharma (International) B.V., Databankweg 26,
3821AL Amersfoort, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1389/001

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 to 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.

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 makes 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.
- 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.**

Children and adolescents

Epidyolex must not be given to children under the age of 2 years, since there is no information on use in children below this age.

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, lamotrigine, lorazepam, midazolam, phenytoin, stiripentol and valproate that are used to treat seizures
- 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)
- bupropion (a medicine to help stop smoking or for treating obesity)
- 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). (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.

This medicinal product contains 10% by volume ethanol (alcohol), i.e. up to 700 mg per dose (for an adult weighing 70 kg), equivalent to 14 millilitres (ml) of beer, or 6 ml of wine per dose.

The medicine may be harmful for those suffering from alcoholism. The alcohol content should be taken into account in pregnant women, children and high-risk groups such as patients with liver disease.

Effects of alcohol in children under the age of 6 years old may include sleepiness, behavioural changes, and problems with concentration and taking part in school activities.

3. How to 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.

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

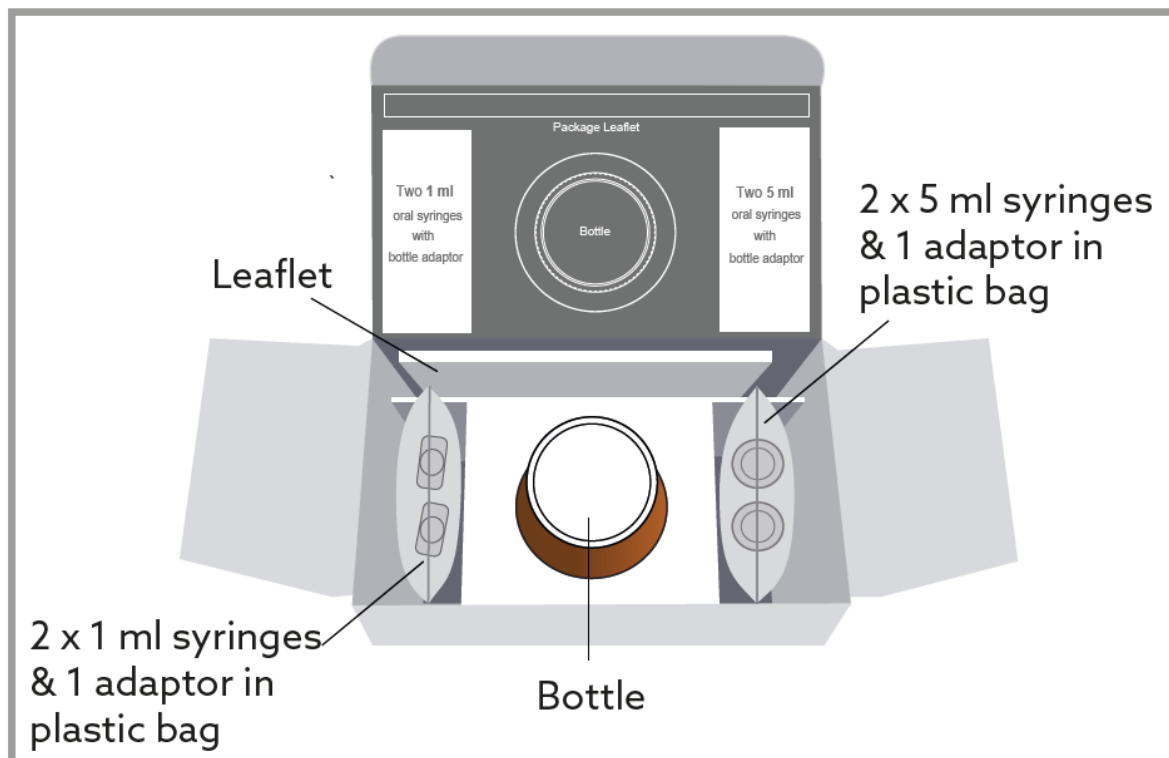
Do not reduce the dose or stop this medicine unless the doctor tells you to.

Instructions for the oral use of Epidyolex

The 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

A spare syringe of each size is provided in the pack in case the first one is damaged or lost.

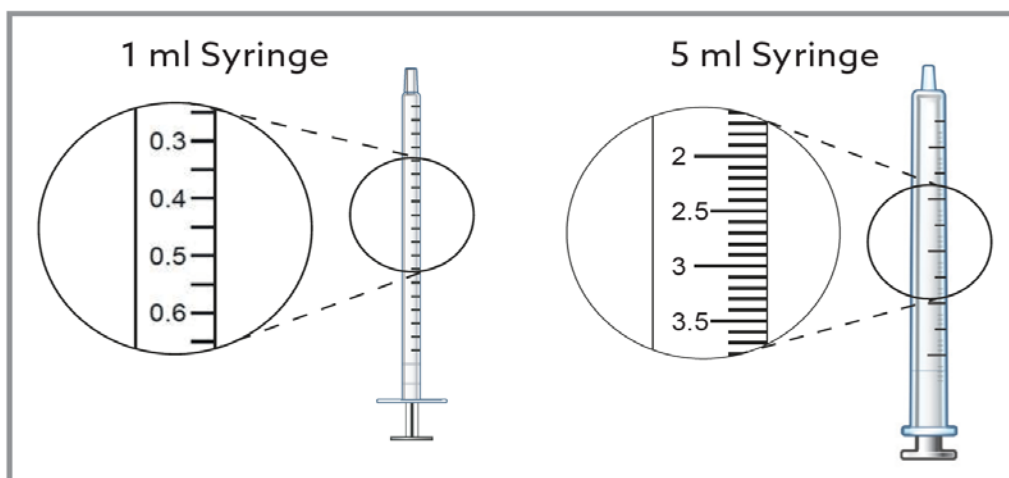


1. Open the bag containing the correct oral syringe to measure your dose.

- 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 adapter should be discarded from the pack unless your doctor or pharmacist tells you to keep both syringes until your final dose has been reached.



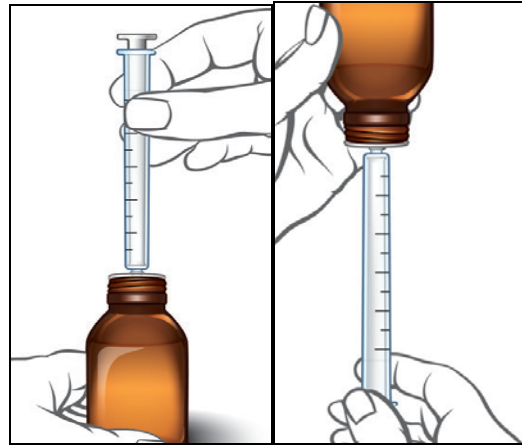
2. Remove the child-resistant cap on the bottle by pushing the cap down whilst turning the cap anti-clockwise.



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.

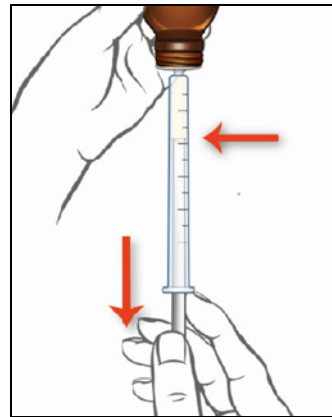


4. Insert the tip of the correct oral syringe fully into the bottle adaptor, and with the oral syringe in place, turn the bottle upside down.

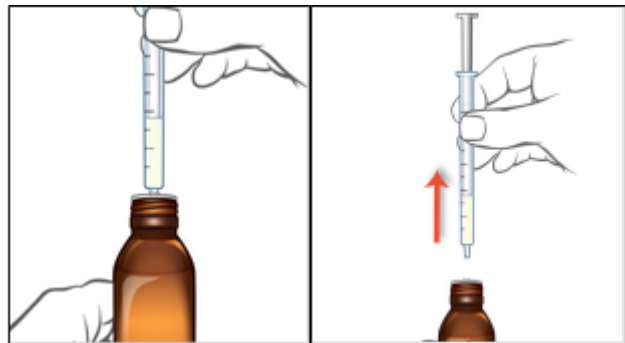


5. Slowly pull back the plunger of the syringe, so the volume (number of ml) of solution needed is drawn into the syringe. Line up the end of the plunger with the volume marking required, as shown opposite.

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.

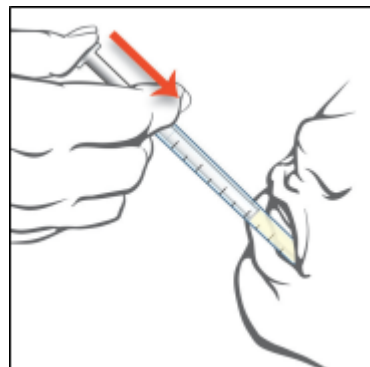


6. Turn the bottle the right side up, and carefully remove the oral syringe from the adaptor.



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.

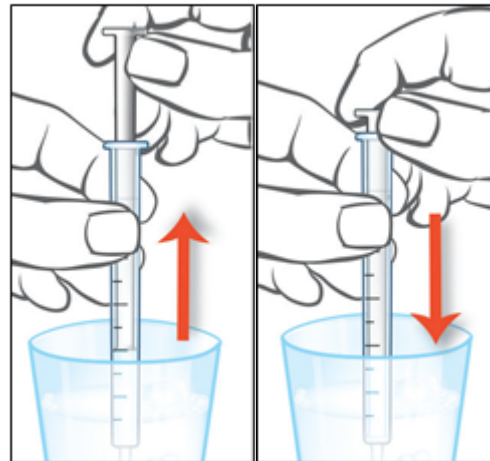
If the dose is more than 5 ml, repeat Steps 4 to 7 to give the remaining dose using the 5 ml oral syringe.



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.



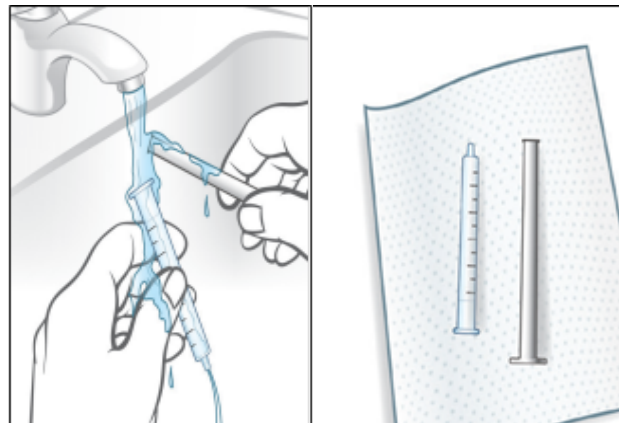
9. Fill a cup with warm soapy water and clean the oral syringe by drawing water in and out using the plunger.



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. 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**:

- High liver enzymes (transaminases elevations) seen in blood tests, which can be a sign of liver injury, have been reported in patients receiving Epidyolex
- 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
- decreased appetite
- diarrhoea
- fever
- feeling tired
- vomiting

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

- lack of energy
- cold, sore throat
- respiratory tract infections (pneumonia, bronchitis)
- blood tests showing increases in levels of certain liver enzymes (which may be signs of liver damage)
- shaking of the body or parts of it
- feeling bad-tempered (irritable, aggressive)
- difficulty in sleeping
- cough
- rash
- increased appetite, weight loss
- drooling
- urinary tract infection
- agitation
- abnormal behaviour

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 8 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).

What Epidyolex looks like and contents of the pack

Epidyolex is a clear, colourless to yellow oral solution. It comes in a bottle which has a child-resistant cap, together with two identical 5 ml or 1 ml oral dosing syringes and two bottle adaptors for using these syringes. The 5 ml syringes are graduated in 0.1 ml and the 1 ml in 0.05 ml increments.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.