

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>Pr</sup>**EPIDIOLEX**<sup>®</sup>

Cannabidiol Oral Solution  
Solution, 100 mg/mL, Oral

Antiepileptic

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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

EPIDIOLEX® (cannabidiol oral solution) is indicated for:

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

#### **1.1 Pediatrics**

Pediatrics (<2 years of age): The safety and efficacy of EPIDIOLEX in pediatric patients <2 years of age have not been established (see [14 CLINICAL TRIALS](#)). Therefore, Health Canada has not authorized an indication for patients <2 years of age.

#### **1.2 Geriatrics**

Geriatrics (≥65 years of age): The safety and efficacy of EPIDIOLEX in patients ≥65 years of age have not been studied as clinical studies of EPIDIOLEX did not include patients aged 65 years and over. It is not known whether geriatric patients would respond differently than younger adult patients. Dose selection 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 drug therapy.

### **2 CONTRAINDICATIONS**

EPIDIOLEX is contraindicated for use in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- patients with transaminase elevations greater than 3 times the upper limit of normal (ULN) and concurrent elevations of bilirubin greater than 2 times the ULN.

### **4 DOSAGE AND ADMINISTRATION**

#### **4.1 Dosing Considerations**

- EPIDIOLEX is to be administered orally.
- EPIDIOLEX is to be titrated according to patient response. Weekly titration is recommended to allow monitoring of individual response and tolerability.
- Titration should not be faster than every other day, which was the titration schedule evaluated in clinical trials.
- The weekly titration schedule is based on pharmacokinetic modelling and simulation. Comparable exposures are predicted from both titration schedules through 10 mg/kg/day, but initial (weeks 2-4) lower exposures are predicted beyond this dose range for the weekly titration schedule.
- Dose(s) of existing antiepileptic regimen to remain stable during treatment initiation and titration.
- Because of the risk of hepatocellular injury, obtain serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and total bilirubin levels in all

patients prior to starting treatment with EPIDIOLEX and at 1 month, 3 months and 6 months post-treatment initiation and then as clinically indicated (see [7 Hepatic/Biliary/Pancreatic](#)).

- Upon changes in EPIDIOLEX dose, this monitoring schedule (1, 3, and 6 months) should be restarted.
- Dosage adjustment is recommended in patients with moderate or severe hepatic impairment (see [4.2 Discontinuation of EPIDIOLEX](#)).
- Discontinue EPIDIOLEX in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 1.5 times the ULN. Patients with sustained transaminase elevations of greater than 5 times the ULN should also have treatment discontinued (see [7 Hepatic/Biliary/Pancreatic](#)).

## 4.2 Recommended Dose and Dosage Adjustment

### Dosing for Seizures Associated with Lennox-Gastaut Syndrome or Dravet Syndrome

The recommended starting dose of EPIDIOLEX is 2.5 mg/kg taken twice daily (5 mg/kg/day).

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). For patients in whom a more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dose may be increased no more frequently than every other day.

Any dose increases above 10 mg/kg/day, up to the maximum recommended daily dose of 20 mg/kg/day, should be made considering individual benefit and risk and with adherence to the full monitoring schedule (see [7 Monitoring and Laboratory Tests](#)).

### Dosing for Seizures Associated with Tuberous Sclerosis Complex

The recommended starting dose of EPIDIOLEX is 2.5 mg/kg taken twice daily (5 mg/kg/day).

After one week, the dosage should be increased to 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). For patients in whom a more rapid titration to 25 mg/kg/day is warranted, the dose may be increased no more frequently than every other day. The efficacy of doses lower than 12.5 mg/kg twice daily has not been studied in patients with TSC.

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 [7 Monitoring and Laboratory Tests](#)).

### Patients with Hepatic Impairment

Dose adjustment is required in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. See [Table 1](#); see also [7 Hepatic/Biliary/Pancreatic](#) and [10.3 Special Populations and Conditions](#).

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

**Table 1: 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 Daily Dose For LGS and DS	Maximal Recommended Daily Dose For TSC
<b>Moderate</b>	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)
<b>Severe</b>	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)

Monitoring of liver function should occur at baseline, 1 month, 3 months, and 6 months after initiation of treatment with EPIDIOLEX. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with EPIDIOLEX, as appropriate (see [7 General](#)).

#### **Patients with Renal Impairment**

There is no requirement for dose modification of EPIDIOLEX in patients with any degree of renal impairment. EPIDIOLEX has not been studied in patients with end-stage renal disease or those undergoing dialysis.

#### **Discontinuation of EPIDIOLEX**

When discontinuing EPIDIOLEX, the dose should be decreased gradually. As with most antiepileptic drugs (AEDs) abrupt discontinuation should be avoided when possible to minimize the risk of increased seizure frequency and status epilepticus (see [7 General](#)). In clinical trials, EPIDIOLEX 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.

#### **4.4 Administration**

Food affects EPIDIOLEX absorption significantly, thus EPIDIOLEX should be taken consistently with food (preferably with the same type of meal) or consistently without food (see [10.3 Pharmacokinetics](#) and [9.5 Drug-Food Interactions](#)).

Calibrated measuring devices (1 mL and 5 mL oral syringes) will be provided and are recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

Oral administration is recommended. When necessary, EPIDIOLEX can be enterally administered via silicone feeding tubes, such as nasogastric or gastrostomy tubes. The recommended volume for flushing (with room temperature drinking water) after each dose is approximately 5 times the priming volume of the tube. The flushing volume may need to be modified in patients with fluid restrictions. Do not use with tubes made of polyvinyl chloride (PVC) or polyurethane and avoid use of silicone nasogastric tubes with short lengths and narrow diameters (e.g., less than 50 cm and less than 5 French).

Discard any unused EPIDIOLEX remaining 12 weeks after first opening the bottle (see [11 STORAGE, STABILITY AND DISPOSAL](#)).

#### 4.5 Missed Dose

If any dose is missed, the missed dose should not be taken. Instead, the next scheduled dose should be taken. Doses should not be doubled. In the case of more than 7 days missed doses, re-titration to the therapeutic dose should be made.

### 5 OVERDOSAGE

Experience with doses higher than the recommended therapeutic dose is limited. Mild diarrhea 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.

Symptomatic and supportive treatment should be given following overdose with EPIDIOLEX, including monitoring of vital signs and observation of the clinical status of the patient. It is not known if EPIDIOLEX is dialysable.

For management of a suspected drug overdose, contact your regional poison control centre.

### 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Solution 100 mg/mL  Each mL of solution contains 100 mg of cannabidiol.	Ethanol anhydrous (10% v/v) Sesame seed oil Strawberry flavouring Sucralose

EPIDIOLEX is a strawberry-flavoured, clear, colourless to yellow solution supplied in an amber glass bottle with a child-resistant closure. EPIDIOLEX is available in bottles containing 60 mL or 100 mL of oral solution. Not all bottle sizes may be marketed.

One bottle of EPIDIOLEX is packaged in a carton with two 1 mL calibrated oral dosing syringes, two 5 mL calibrated oral dosing syringes, bottle adapters, and a patient medication information leaflet.

### 7 WARNINGS AND PRECAUTIONS

#### General

#### Somnolence and Sedation

EPIDIOLEX can cause somnolence and sedation. In controlled studies for LGS and DS (10 and 20 mg/kg/day dosages), the incidence of somnolence and sedation (including lethargy) was 31% in EPIDIOLEX-treated patients (27% and 33% of patients taking EPIDIOLEX 10 or 20 mg/kg/day, respectively), compared with 12% in patients receiving placebo, and was generally dose-related. The

rate was higher in patients on concomitant clobazam (44% in EPIDIOLEX-treated patients taking clobazam compared with 14% in EPIDIOLEX-treated patients not on clobazam). In the controlled study for TSC, the incidence of somnolence and sedation including lethargy was 19% in EPIDIOLEX-treated patients (25mg/kg/day) compared with 17% of patients on placebo. The rate was higher in patients on concomitant clobazam (33% in EPIDIOLEX-treated patients taking clobazam compared with 14% in EPIDIOLEX-treated patients not on clobazam). In general, these effects were more common early in treatment and may diminish with continued treatment. Other CNS depressants, including alcohol, can potentiate the somnolence and sedation effect of EPIDIOLEX. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX to gauge whether it adversely affects their ability to drive or operate machinery (see [7 Driving and Operating Machinery](#)).

#### Discontinuation of EPIDIOLEX

EPIDIOLEX should be decreased gradually to minimise the risk of increased seizure frequency and status epilepticus (see [4.2 Recommended Dose and Dosage Adjustment](#)). If prompt withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered and transition to another antiepileptic drug should be made under close medical supervision.

#### **Driving and Operating Machinery**

EPIDIOLEX can cause somnolence and sedation. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX to gauge whether it adversely affects their ability to drive or operate machinery (see [7 Somnolence and Sedation](#)).

#### **Hepatic/Biliary/Pancreatic**

##### Hepatocellular Injury

EPIDIOLEX can cause dose-related elevations of liver transaminases (ALT and/or AST). In controlled studies for LGS, DS, and TSC (10, 20, and 25 mg/kg/day dosages), the incidence of ALT elevations above 3 times the upper limit of normal (ULN) was 12% in EPIDIOLEX-treated patients compared with <1% in patients on placebo. Two cases met the modified Hy's Law (hepatic AST or ALT  $\geq$  3 times ULN, and total bilirubin  $\geq$  1.5 times ULN). The patients continued their respective treatments and their abnormal liver laboratory tests resolved without intervention. There were no patients that experienced concurrent bilirubin elevations more than 1.5 times the ULN or more. Liver enzyme elevations have been observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate.

##### *Concomitant Valproate and Clobazam*

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. Discontinuation or dose adjustment of valproate or clobazam should be considered if transaminase elevations occur (see [9.4 Drug-Drug Interactions](#)). Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX or reduction of EPIDIOLEX 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 EPIDIOLEX, without dose reduction.

##### *Dose*

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



## Monitoring and Laboratory Tests

In general, transaminase elevations of greater than 3 times the ULN in the presence of elevated bilirubin ( $\geq 1.5$  times the ULN) without an alternative explanation are an important predictor of severe liver injury. Early identification of elevated liver enzymes may decrease the risk of a serious outcome. Patients with elevated baseline transaminase levels above 3 times the ULN, accompanied by elevations in bilirubin ( $\geq 1.5$  times the ULN), should be evaluated prior to initiation of EPIDIOLEX treatment.

Prior to starting treatment with EPIDIOLEX obtain serum transaminases and total bilirubin levels. Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months and 6 months after initiation of treatment with EPIDIOLEX, and periodically thereafter or as clinically indicated. Serum transaminases and total bilirubin levels should also be obtained within 1 month following changes in EPIDIOLEX dose and addition of or changes in medications that are known to impact the liver (see [9.4 Drug-Drug Interactions](#)).

In patients with identified baseline elevations of liver enzymes or 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 EPIDIOLEX, and periodically thereafter or as clinically indicated. Upon changes in EPIDIOLEX dose 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 of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with EPIDIOLEX, as appropriate. Discontinue EPIDIOLEX in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 1.5 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 (see [4.2 Recommended Dose and Dosage Adjustment](#)). Consider dosage adjustment of any co-administered medication that is known to affect the liver (e.g., valproate and clobazam).

## Immune

### Hypersensitivity

EPIDIOLEX can cause hypersensitivity reactions. Patients with known or suspected hypersensitivity to any ingredients of EPIDIOLEX were excluded from phase I to III clinical trials. If a patient develops hypersensitivity reaction after treatment, the drug should be discontinued. EPIDIOLEX is contraindicated in patients with a prior hypersensitivity to cannabidiol or to any of the ingredients in the product, which includes sesame seed oil (see [2 CONTRAINDICATIONS](#)).

In the clinical safety datasets, there were six cases of skin rashes with eosinophilia, two of which also had hepatic enzyme increases. There was one further case with all three events but the events had no time overlap. None of the cases met the diagnostic criteria of Drug Reaction with Eosinophilia and Systemic Syndromes (DRESS), with various investigator-implemented clinical management.

## Psychiatric

### Suicidal Ideation and Behaviour

Suicidal Ideation and Behaviour have been reported in patients treated with antiepileptic agents in several indications. All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be

considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. An FDA meta-analysis of randomized placebo-controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known. There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Anyone considering prescribing EPIDIOLEX or any other AED must balance the risk of suicidal thoughts or behaviours with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

## **Reproductive Health: Female and Male Potential**

- **Fertility**

In a fertility and early embryonic development study in rat, no effect on reproductive ability of males or females was noted up to an oral dose of 250 mg/kg/day CBD. No changes were noted in effects on male or female reproductive indices, male reproductive organ weights, or female estrus cycling. No effects were noted on mating or fertility (see [16 Reproductive and Developmental Toxicology](#)).

Women of childbearing potential and fertile men should take reliable contraceptive precautions (see [16 Reproductive and Developmental Toxicology](#)).

### **7.1 Special Populations**

#### **7.1.1 Pregnant Women**

There are only limited data from the use of EPIDIOLEX in pregnant women. Studies in animals have shown reproductive toxicity (see [16 Reproductive and Developmental Toxicology](#)). As a precautionary measure, EPIDIOLEX should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the fetus.

#### Pregnancy Exposure Registry

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of AEDs during

pregnancy. To enroll, patients can call the toll-free number, 1-888-233-2334. Information on the registry can also be found at the website <https://www.aedpregnancyregistry.org/>.

### **7.1.2 Breastfeeding**

There are no data on the presence of EPIDIOLEX or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EPIDIOLEX and any potential adverse effects on the breastfed infant from EPIDIOLEX or from the underlying maternal condition.

### **7.1.3 Pediatrics**

The safety and efficacy of EPIDIOLEX in pediatric patients <2 years of age have not been established.

Administration of cannabidiol to juvenile rats resulted in neuro-behavioural effects, increased bone mineral density, liver hepatocyte vacuolation and delayed male sexual maturation (see [16 Juvenile Toxicology](#)).

### **7.1.4 Geriatrics**

Clinical trials of EPIDIOLEX in the treatment of LGS, DS, and TSC did not include any patients ≥65 years or above. It is not known whether geriatric patients would respond differently than younger adult patients. Dose selection for these patients 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 drug therapy.

## **8 ADVERSE REACTIONS**

### **8.1 Adverse Reaction Overview**

#### Patients with Dravet Syndrome

A total of 221 individual patients were exposed to EPIDIOLEX during the controlled clinical trials of up to 14 weeks duration. In the controlled clinical trials, the incidence of serious adverse events was 19.9% with EPIDIOLEX and 10.7% in the placebo group. The most commonly observed serious adverse events in patients receiving EPIDIOLEX were status epilepticus, pneumonia and seizure. In the controlled clinical trials, the most frequent cause of discontinuation of treatment in patients receiving cannabidiol (EPIDIOLEX) was somnolence (3.2%) and transaminase elevations (3.2%). The incidence of discontinuation due to transaminase elevations was dose dependent. Risk factors for transaminase elevation include concomitant valproate and clobazam, dose of EPIDIOLEX, and baseline transaminase elevations.

The most common adverse reactions that occurred in EPIDIOLEX-treated patients with DS (incidence at least 5% and a difference of ≥2% than placebo) are somnolence and sedation (30%), decreased appetite (24%), diarrhea (22%), pyrexia (20%), fatigue (15%) and vomiting (12%) (see [Table 3](#) for detailed data).

### Patients with Lennox-Gastaut Syndrome

A total of 235 individual patients were exposed to EPIDIOLEX during the controlled clinical trials of up to 14 weeks duration. In the controlled clinical trials, the incidence of serious adverse events was 19.6% with EPIDIOLEX and 7.5% in the placebo group. The most commonly observed serious adverse events in patients receiving EPIDIOLEX were status epilepticus, pneumonia and transaminase elevations. In the controlled clinical trials, the most frequent cause of discontinuation of treatment in patients receiving cannabidiol (EPIDIOLEX) was transaminase elevations (4.7%). The incidence of discontinuation due to transaminase elevations was dose dependent. Risk factors for transaminase elevation include concomitant valproate and clobazam, dose of EPIDIOLEX, and baseline transaminase elevations.

The most common adverse reactions that occurred in EPIDIOLEX-treated patients with LGS (incidence at least 5% and a difference of  $\geq 2\%$  than placebo) are somnolence and sedation (27%), decreased appetite (18%) and diarrhea (15%) (see [Table 4](#) for detailed data).

### Patients with Tuberous Sclerosis Complex

A total of 148 individual patients were exposed to EPIDIOLEX during a controlled clinical trial of up to 16 weeks duration. In the controlled clinical trial, the incidence of serious adverse events was 17.6% with EPIDIOLEX and 2.6% in the placebo group. The most commonly observed serious adverse events in patients receiving EPIDIOLEX were transaminase elevations. In the controlled clinical trial, the adverse events most frequently leading to discontinuation was rash (5%).

The most common adverse reactions that occurred in EPIDIOLEX-treated patients with TSC (incidence at least 5% at the recommended dose and a difference of  $\geq 2\%$  greater than placebo) are diarrhea (31%), decreased appetite (20%), pyrexia (18%), vomiting (17%), somnolence (13%), cough (11%), increased liver enzymes (12%), and constipation (11%) (see [Table 5](#) for detailed data).

## **8.2 Clinical Trial Adverse Reactions**

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

### Dravet Syndrome Clinical Trials

In placebo-controlled trials of patients with DS (includes GWPCARE1 [parts A and B] and GWPCARE2), 221 patients received EPIDIOLEX. Adverse reactions are presented below; the duration of treatment in these trials was up to 14 weeks. Approximately 51% of patients were female, 84% were Caucasian, and the mean age was 9 years (range 2 to 18 years). All patients were taking other AEDs.

[Table 3](#) lists the adverse reactions that were reported in DS patients treated with EPIDIOLEX as adjunctive therapy in the Phase 3 controlled trials.

**Table 3: Treatment Emergent Adverse Events Occurring in ≥5% in EPIDIOLEX-treated patients, and at ≥2% higher frequency than placebo, in Randomized Controlled Trials (GWPCARE1 [parts A and B] and GWPCARE2), in Patients with DS**

System Organ Class Preferred Term	EPIDIOLEX			Placebo (n=131) N (%)
	10 mg/kg/day (n=72)	20 mg/kg/day (n=139)	All active (n=221 <sup>b</sup> )	
	N (%)	N (%)	N (%)	
<b>Gastrointestinal Disorders</b>				
Diarrhea	11 (15)	37 (27)	48 (22)	15 (12)
Vomiting	5 (7)	21 (15)	27 (12)	7 (5)
<b>General Disorders and Administration Site Conditions</b>				
Pyrexia	18 (25)	24 (17)	45 (20)	16 (12)
Fatigue	5 (7)	28 (20)	33 (15)	11 (8)
<b>Infections and Infestations</b>				
Pneumonia <sup>a</sup>	7 (10)	7 (5)	14 (6)	3 (2)
<b>Investigations</b>				
Aspartate aminotransferase increased	3 (4)	11 (8)	14 (6)	0
Alanine aminotransferase increased	3 (4)	9 (7)	12 (5)	0
Gamma-glutamyltransferase increased	4 (6)	8 (6)	12 (5)	3 (2)
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite	12 (17)	41 (30)	53 (24)	14 (11)
<b>Nervous System Disorders</b>				
Somnolence and Sedation	20 (28)	42 (30)	66 (30)	16 (12)
<b>Psychiatric Disorders</b>				
Irritability	4 (6)	9 (7)	13 (6)	2 (2)

<sup>a</sup> Grouped Terms: **Pneumonia:** Pneumonia, Pneumonia viral, Aspiration pneumonia

<sup>b</sup> Includes 10 patients randomized to 5 mg/kg/day in GWPCARE1 Part A.

#### Lennox-Gastaut Syndrome Clinical Trials

In placebo-controlled trials of patients with LGS (includes GWPCARE3 and GWPCARE4), 235 patients received EPIDIOLEX. Adverse reactions are presented below; the duration of treatment in these trials was up to 14 weeks. Approximately 45% of patients were female, 87% were Caucasian, and the mean age was 15 years (range 2 to 48 years). All patients were taking other AEDs.

[Table 4](#) lists the adverse reactions that were reported in LGS patients treated with EPIDIOLEX as adjunctive therapy in the Phase 3 controlled trials.

**Table 4: Treatment Emergent Adverse Events Occurring in  $\geq 5\%$  in EPIDIOLEX-treated patients, and at  $\geq 2\%$  higher frequency than placebo, in Randomized Controlled Trials (GWPCARE3 and GWPCARE4) in Patients with LGS**

System Organ Class Preferred Term	EPIDIOLEX			Placebo (n=161) N (%)
	10 mg/kg/day (n=67)	20 mg/kg/day (n=168)	All active (n=235)	
	N (%)	N (%)	N (%)	
<b>Gastrointestinal Disorders</b>				
Diarrhea	7 (10)	28 (17)	35 (15)	13 (8)
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	5 (8)	13 (8)	18 (8)	4 (3)
<b>Infections and Infestations</b>				
Pneumonia <sup>a</sup>	5 (8)	9 (5)	14 (6)	1 (1)
<b>Investigations</b>				
Alanine aminotransferase increased	3 (5)	12 (7)	15 (6)	3 (2)
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite	11 (16)	32 (19)	43 (18)	8 (5)
<b>Nervous System Disorders</b>				
Somnolence and sedation	16 (24)	48 (29)	64 (27)	14 (9)
Lethargy	3 (5)	10 (6)	13 (6)	2 (1)
Status epilepticus	7 (10)	5 (3)	12 (5)	4 (3)
<b>Psychiatric Disorders</b>				
Irritability	6 (9)	6 (4)	12 (5)	3 (2)

<sup>a</sup> Grouped Terms: **Pneumonia:** Pneumonia, Pneumonia mycoplasmal, Pneumonia adenoviral, Aspiration pneumonia, Pneumonia bacterial, Pneumonia respiratory syncytial viral.

#### Tuberous Sclerosis Complex Clinical Trial

In a placebo-controlled trial of patients with TSC (GWPCARE6), 148 patients received EPIDIOLEX. Adverse reactions are presented below; the duration of treatment in this trial was up to 16 weeks. Approximately 42% of patients were female, 90% were Caucasian, and the mean age was 14 years (range 1 to 57 years). All patients but one (25 mg/kg/day group) were taking other AEDs.

[Table 5](#) lists the adverse reactions that were reported in TSC patients treated with EPIDIOLEX as adjunctive therapy, based on the 25 mg/kg/day group in a controlled trial.

**Table 5: Treatment Emergent Adverse Events Occurring in  $\geq 5\%$  in EPIDIOLEX-treated patients, and at  $\geq 2\%$  higher frequency than placebo, in a Randomized Controlled Trial (GWPCARE6) of Patients with TSC**

System Organ Class Preferred Term	EPIDIOLEX	Placebo
	25 mg/kg/day	
	n = 75 N (%)	n = 76 N (%)
<b>Blood and Lymphatic System Disorders</b>		
Anemia	5 (7)	1 (1)
<b>Gastrointestinal Disorders</b>		
Diarrhea	23 (31)	19 (25)
Vomiting	13 (17)	7 (9)
Constipation	8 (11)	6 (8)
Nausea	7 (9)	2 (3)
<b>General Disorders and Administration Site Conditions</b>		
Pyrexia	14 (19)	6 (8)
Fatigue	4 (5)	1 (1)
Gait disturbance	4 (5)	2 (3)
<b>Infections and Infestations</b>		
Urinary tract infection	4 (5)	0 (0)
<b>Investigations</b>		
Gamma glutamyl transferase increased	12 (16)	0 (0)
Alanine aminotransferase increased	9 (12)	0 (0)
Aspartate aminotransferase increased	8 (11)	0 (0)
Weight decreased	5 (7)	0 (0)
Eosinophil count increased	4 (5)	0 (0)
<b>Metabolism and Nutrition Disorders</b>		
Decreased appetite	15 (20)	9 (12)
<b>Nervous System Disorders</b>		

System Organ Class Preferred Term	EPIDIOLEX	Placebo
	25 mg/kg/day	
	n = 75 N (%)	n = 76 N (%)
Somnolence	10 (13)	7 (9)
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	8 (11)	5 (7)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	5 (7)	3 (4)

### *Pneumonia*

Pneumonia has been observed in controlled trials of LGS and DS with clobazam (14% in patients receiving 10 mg/kg/day CBD, 7% in patients receiving 20 mg/kg/day CBD, and 1% receiving placebo) and without concomitant clobazam (0% in patients receiving 10 mg/kg/day CBD, 3% in patients receiving 20 mg/kg/day CBD, and 2% receiving placebo). In patients with TSC receiving 25 mg/kg/day CBD, pneumonia has been observed with concomitant clobazam (17% in patients receiving 25 mg/kg/day CBD and 0% receiving placebo) and without clobazam (0% in patients receiving 25 mg/kg/day CBD and 2% receiving placebo).

### **8.3 Less Common Clinical Trial Adverse Reactions**

The following adverse events were reported in the double-blind, placebo-controlled clinical trials at an incidence <5% in CBD-OS-treated patients in DS/LGS and/or TSC indication, at any CBD-OS dose and at a higher frequency (%) than placebo:

**Blood and lymphatic disorders:** anaemia, eosinophilia, neutropenia

**Cardiac disorders:** tachycardia

**Eye disorders:** diplopia, mydriasis, ocular hyperemia

**Gastrointestinal disorders:** abdominal distension, abdominal pain, abdominal pain upper, dry mouth, dyspepsia, eructation, frequent bowel movements, hemochezia, mouth ulceration, nausea, retching

**General disorder and administration site conditions:** asthenia, crying, feeling abnormal, feeling drunk, gait disturbance, malaise, peripheral swelling

**Immune system disorders:** hypersensitivity, skin rash and eosinophilia

**Infections and infestations:** adenovirus infection, bronchitis, candida infection, conjunctivitis, ear infection, erythema infectiosum, eye infection, fungal infection, gastroenteritis, gastroenteritis viral, gingivitis, herpes simplex, hordeolum, influenza, laryngitis, oral candidiasis, otitis externa, pharyngitis streptococcal, pneumonia, respiratory syncytial virus infection, respiratory tract infection, sepsis, staphylococcal infection, tonsillitis, urinary tract infection, viral infection, viral rash, viral upper respiratory tract infection

**Injury, poisoning and procedural complications:** hand fracture, ligament sprain, skin abrasion, skin injury, tooth fracture, toxicity to various agents, upper limb fracture, wound

**Investigations:** anticonvulsant drug level increased, blood bilirubin increased, blood creatinine phosphokinase increased, culture urine positive, eosinophil count increased, hepatic enzyme increased, international normalised ratio increased, neutrophil count decreased, platelet count decreased, prothrombin time prolonged, red blood cell count decreased, respiratory rate increased, transaminases



increased, urine output decreased, urine output increased, weight decreased, white blood cell count decreased

**Metabolism and nutrition disorders:** dehydration, diet refusal, fluid intake reduced, hypertriglyceridemia, hypophagia, increased appetite

**Musculoskeletal and connective disorders:** muscle spasms, muscle twitching, musculoskeletal pain

**Nervous System disorders:** ataxia, atonic seizures, balance disorder, coordination abnormal, drooling, dysarthria, generalised tonic-clonic seizure, hypersomnia, hypotonia, myoclonus, poor quality sleep, sedation, slow response to stimuli, tonic convulsion, tremor

**Psychiatric disorders:** abnormal behaviour, aggression, agitation, anger, anxiety, apathy, bruxism, communication disorder, depressed mood, disorientation, inappropriate affect, insomnia, mood swings, oppositional defiant disorder, panic attack, restlessness, sleep disorder

**Renal disorders and urinary disorders:** urinary retention

**Reproductive system and breast disorders:** metrorrhagia

**Respiratory, thoracic and mediastinal disorders:** acute respiratory failure, asthma, hypoxia, oropharyngeal pain, pneumonia aspiration, respiratory disorder, respiratory distress, respiratory failure, rhinorrhea, rhonchi, sleep apnea syndrome, throat irritation, upper respiratory tract congestion, wheezing

**Skin and subcutaneous tissue disorders:** decubitus ulcer, pruritus, rash erythematous, rash generalised, rash macular, rash maculo-papular, urticaria

**Vascular disorders:** hypertension, hypotension, pallor, peripheral coldness

#### 8.4 Abnormal laboratory findings: hematologic, clinical chemistry and other quantitative data

[Table 6](#) lists Abnormal laboratory findings in placebo-controlled studies in LGS, DS, or TSC patients treated with EPIDIOLEX as adjunctive therapy in the Phase 3 controlled trials.

**Table 6: Abnormal biochemistry laboratory findings in placebo-controlled studies in LGS, DS, or TSC patients**

	10 mg/kg/day N=139 n/N (%)	20 mg/kg/day N=307 n/N (%)	25 mg/kg/day N=75 n/N (%)	Placebo N=368 n/N (%)
ALT $\geq 3 \times$ ULN	4/131 (3)	47/296 (16)	9/75 (12)	2/359 (1)
ALT $\geq 3 \times$ ULN and total bilirubin $\geq 1.5 \times$ ULN	0/131	0/298	1/75 (1)	0/361
Creatinine increase $>10\%$ , from baseline to Week 2 (Jaffe method)	41/120 (34)	121/267 (40)	14/44 (32)	98/319 (31)
Creatinine increase $>10\%$ from baseline, at any point during treatment (Jaffe method)	92/133 (69)	213/299 (71)	30/46 (65)	206/340 (61)

**Table 7: Abnormal hematology laboratory findings in placebo-controlled studies in LGS, DS, or TSC patients**

	10 mg/kg/day N=139 n/N (%)	20 mg/kg/day N=307 n/N (%)	25 mg/kg/day N=75 n/N (%)	Placebo N=368 n/N (%)
Hemoglobin shift from normal (baseline) to low (on treatment)	30/139 (22)	73/307 (24)	23/75 (31%)	45/368 (12)
Platelet count decrease	10/132 (8)	20/272 (7)	6/72 (8)	11/343 (3)

**Table 8: Other abnormal quantitative physical examination findings in placebo-controlled studies in LGS, DS, or TSC patients**

	10 mg/kg/day N=139 n/N (%)	20 mg/kg/day N=307 n/N (%)	25 mg/kg/day N=75 n/N (%)	Placebo N=368 n/N (%)
Weight decreased ≥5%	10/139 (7)	57/307 (19)	23/75 (31)	31/368 (8)

#### *Hematologic Abnormalities*

EPIDIOLEX can cause decreases in hemoglobin and hematocrit. In patients with LGS, DS, and TSC, the mean decrease in hemoglobin from baseline in end-of-treatment was -0.36 g/dL in EPIDIOLEX-treated patients receiving 10, 20 or 25 mg/kg/day. A corresponding decrease in hematocrit was also observed, with a mean change of -1.3% in EPIDIOLEX-treated patients.

Twenty-seven percent (27%) of EPIDIOLEX-treated patients with LGS and DS and 38% of EPIDIOLEX-treated patients (25mg/kg/day) with TSC developed a new laboratory-defined anemia during the course of the study (defined as a normal hemoglobin concentrations at baseline, with a reported value less than the lower limit of normal at a subsequent time point).

#### *Increases in Creatinine*

EPIDIOLEX 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 EPIDIOLEX. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS, DS, or TSC.

#### *Decreased Weight*

EPIDIOLOX can cause weight loss or decreased weight gain. In patients with LGS, DS, and TSC, the decrease in weight appeared to be dose dependent, with 21% of patients on EPIDIOLEX 20 or 25mg/kg/day experiencing a decrease in weight of ≥5%, compared to 7% in patients on EPIDIOLEX 10mg/kg/day. In some cases, the decreased weight was reported as an adverse event.

## 8.5 Post-Market Adverse Reactions

The adverse event profile, based on post-market spontaneous reports, is consistent with those observed in clinical trials.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

CBD is a substrate for cytochrome P450 (CYP)3A4 and CYP2C19. Consider an increase in EPIDIOLEX dosage when coadministered with a strong CYP3A4 and/or CYP2C19 inducer (see [9.4 Drug-Drug Interactions](#)).

CBD has the potential to inhibit uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes UGT1A9, UGT2B7, CYP1A2, CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations. Consider a reduction in dosage of the substrates, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX (see [9.4 Drug-Drug Interactions](#)).

### 9.3 Drug-Behavioural Interactions

Concomitant use of EPIDIOLEX with alcohol will likely increase the risk of sedation and somnolence (see [7 General](#)).

### 9.4 Drug-Drug Interactions

**Table 9: Effect of Other Drugs on EPIDIOLEX**

Co-administered Drug	Source of Evidence		Dose Schedule	Effect on EPIDIOLEX Pharmacokinetics		Recommendation
		EPIDIOLEX		Co-administered Drug	C <sub>max</sub> (Geometric mean ratio [90% confidence intervals])	
<b>Antiepileptic Drugs (AEDs)</b>						
Clobazam	HV CT	750 mg BID EPIDIOLEX	5 mg BID clobazam	Cannabidiol: 1.34 (0.93, 1.95) 7-hydroxy- cannabidiol: 1.73 (1.36, 2.20)	Cannabidiol: 1.30 (1.00, 1.70) 7-hydroxy- cannabidiol: 1.47 (1.26, 1.70)	
Stiripentol	HV CT	750 mg BID EPIDIOLEX	750 mg BID stiripentol	Cannabidiol: 1.13 (0.96, 1.33) 7-hydroxy- cannabidiol: 0.71 (0.51, 0.99)	Cannabidiol: 1.03 (0.94, 1.14) 7-hydroxy- cannabidiol: 0.72 (0.61, 0.85)	

Co-administered Drug	Source of Evidence		Dose Schedule	Effect on EPIDIOLEX Pharmacokinetics		Recommendation
		EPIDIOLEX		Co-administered Drug	C <sub>max</sub> (Geometric mean ratio [90% confidence intervals])	
Valproate	HV CT	750 mg BID EPIDIOLEX	500 mg BID valproate	Cannabidiol: 0.74 (0.58, 0.93) 7-hydroxy-cannabidiol: 0.97 (0.67, 1.41)	Cannabidiol: 1.05 (0.90, 1.24) 7-hydroxy-cannabidiol: 1.22 (0.96, 1.55)	Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. If such elevations occur, discontinuation or reduction of EPIDIOLEX and/or concomitant valproate should be considered. Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic drugs and EPIDIOLEX.
POPPK report on [Clobazam, levetiracetam, topiramate, rufinamide, lamotrigine] No statistically significant effect of any of these medications was observed on any CBD PK parameter in POPPK model from LGS patients and pooled POPPK model using data from HV and patient studies.						
<b>CYP2C19 Inhibitors</b>						
Fluconazole	HV CT	750 mg single doses EPIDIOLEX	400 mg single dose then 200 mg once daily fluconazole	Cannabidiol: 1.24 (1.05, 1.47) 7-hydroxy-cannabidiol: 0.59 (0.48, 0.72)	Cannabidiol: 1.21 (1.08, 1.36) 7-hydroxy-cannabidiol: 0.71 (0.61, 0.82)	
<b>CYP2C19 Inducers</b>						
Rifampicin	HV CT	750 mg single doses EPIDIOLEX	600 mg once daily rifampicin	Cannabidiol: 0.66 (0.56, 0.78) 7-hydroxy-cannabidiol: 0.33 (0.29, 0.38)	Cannabidiol: 0.68 (0.61, 0.75) 7-hydroxy-cannabidiol: 0.37 (0.33, 0.41)	When co-administered with a strong CYP2C19 inducer, based on clinical response and tolerability, EPIDIOLEX dose may be up-titrated by up to 2-fold.
<b>CYP3A4 Inhibitors</b>						
Itraconazole	HV CT	750 mg single doses EPIDIOLEX	600 mg once daily rifampicin	Cannabidiol: 1.01 (0.82, 1.25) 7-hydroxy-cannabidiol: 1.06 (0.90, 1.25)	Cannabidiol: 1.05 (0.96, 1.15) 7-hydroxy-cannabidiol: 1.17 (1.07, 1.27)	

Co-administered Drug	Source of Evidence		Dose Schedule	Effect on EPIDIOLEX Pharmacokinetics		Recommendation
		EPIDIOLEX		Co-administered Drug	C <sub>max</sub> (Geometric mean ratio [90% confidence intervals])	
<b>CYP3A4 Inducers</b>						
Rifampicin	HV CT	750 mg single doses EPIDIOLEX	600 mg once daily rifampicin	Cannabidiol: 0.66 (0.56, 0.78) 7-hydroxy-cannabidiol: 0.33 (0.29, 0.38)	Cannabidiol: 0.68 (0.61, 0.75) 7-hydroxy-cannabidiol: 0.37 (0.33, 0.41)	When co-administered with a strong CYP3A4 inducer, based on clinical response and tolerability, EPIDIOLEX dose may be up-titrated by up to 2-fold.

Legend: BID = twice daily; HV CT = clinical trial with healthy volunteers; POPPK = population pharmacokinetics; Pt CT = clinical trial with patients.

**Table 10: Effect of EPIDIOLEX on Other Drugs**

Co-administered Drug	Source of Evidence	Dose Schedule		Effect on Co-administered Drug Pharmacokinetics		Recommendation
		Co-administered Drug	EPIDIOLEX	C <sub>max</sub> (Geometric mean ratio [90% CI])	AUC (Geometric mean ratio [90% CI])	
<b>Antiepileptic Drugs (AEDs)</b>						
Clobazam	HV CT and Pt CT	5 mg BID clobazam (HV)  Individual stable clobazam treatment regimens (Pt)	Range: 0.5 to 10 mg/kg BID EPIDIOLEX	Clobazam: 1.00 (0.83, 1.19) to 1.20 (1.05, 1.38)  N-desmethylclobazam: 2.22 (1.42, 3.46) to 3.39 (2.61, 4.39)	Clobazam: 1.06 (0.90, 1.24) to 1.21 (1.05, 1.39)  N-desmethylclobazam: 2.64 (1.95, 3.58) to 3.38 (2.62, 4.36)	The increase in N-desmethylclobazam may increase the risk of clobazam-related adverse reactions (see 8 ADVERSE REACTIONS; 7 WARNINGS AND PRECAUTIONS). Consider a reduction in dosage of clobazam if adverse reactions known to occur with clobazam are experienced when coadministered with EPIDIOLEX.
Stiripentol	HV CT	750 mg BID stiripentol	750 mg BID EPIDIOLEX	Stiripentol: 1.28 (1.08, 1.52)	Stiripentol: 1.55 (1.42, 1.69)	The mechanism of this minor interaction has not been determined. The clinical relevance of this effect is unknown, but patients should be monitored for adverse drug reactions
	Pt CT	Individual stable stiripentol treatment regimens	10 mg/kg BID EPIDIOLEX	Stiripentol: 1.17 (1.03, 1.33)	Stiripentol: 1.30 (1.09, 1.55)	
Valproate	HV CT	500 mg BID valproate	750 mg BID EPIDIOLEX	Valproate: 1.01 (0.95, 1.07)	Valproate: 0.99 (0.90, 1.08)	Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme

Co-administered Drug	Source of Evidence	Dose Schedule		Effect on Co-administered Drug Pharmacokinetics		Recommendation
		Co-administered Drug	EPIDIOLEX	C <sub>max</sub> (Geometric mean ratio [90% CI])	AUC (Geometric mean ratio [90% CI])	
	Pt CT	Individual stable valproate treatment regimens	10 mg/kg BID EPIDIOLEX	Valproate: 0.87 (0.79, 0.95) 2-propyl-4-pentenoic acid: 0.77 (0.66, 0.90)	Valproate: 0.83 (0.75, 0.92) 2-propyl-4-pentenoic acid: 0.70 (0.62, 0.80)	elevations. If such elevations occur, discontinuation or reduction of EPIDIOLEX and/or concomitant valproate should be considered. Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic drugs and EPIDIOLEX
Lamotrigine	In vitro	In vitro data predict drug-drug interactions with UGT2B7 substrates (e.g., lamotrigine) when co-administered with EPIDIOLEX.				Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of CYP2C9 and UGT2B7, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX.
Phenytoin	In vitro	Coadministration of EPIDIOLEX is predicted to cause clinically significant interactions with CYP2C9 substrates (e.g., phenytoin).				
Everolimus	HV CT	Single doses 5 mg everolimus	12.5 mg/kg BID EPIDIOLEX	Everolimus: 2.50 (2.12, 2.94)	Everolimus: 2.45 (2.15, 2.80)	When initiating EPIDIOLEX in patients taking everolimus, monitor therapeutic drug levels of everolimus and adjust the dosage accordingly. When initiating everolimus in patients taking a stable dosage of EPIDIOLEX, a lower starting dose of everolimus is recommended, with therapeutic drug monitoring.
<b>CYP2C19 Substrates</b>						
Eg, diazepam, omeprazole, clobazam	CT	See AEDs, clobazam				In vivo data show that coadministration of EPIDIOLEX increases plasma concentrations of drugs that are metabolized by (i.e., are substrates of) CYP2C19 (e.g., diazepam) and may increase the risk of adverse reactions with these substrates (see 10 CLINICAL PHARMACOLOGY, Pharmacokinetics). Consider a reduction in dosage of sensitive CYP2C19 substrates, as clinically appropriate, when coadministered with EPIDIOLEX.

Co-administered Drug	Source of Evidence	Dose Schedule		Effect on Co-administered Drug Pharmacokinetics		Recommendation
		Co-administered Drug	EPIDIOLEX	C <sub>max</sub> (Geometric mean ratio [90% CI])	AUC (Geometric mean ratio [90% CI])	
<b>CYP3A4 Substrates</b>						
Midazolam	HV CT	Single doses 2.5 mg midazolam	750 mg BID EPIDIOLEX	Midazolam: 0.80 (0.67, 0.96) 1'- hydroxymidazolam: 1.12 (0.93, 1.34)	Midazolam: 0.92 (0.78, 1.09) 1'- hydroxymidazolam: 1.68 (1.41, 2.01)	
<b>CYP2C8 and CYP2C9 Substrates</b>						
e.g., repaglinide, warfarin, phenytoin	In vitro	Coadministration of EPIDIOLEX is predicted to cause clinically significant interactions with CYP2C8 and CYP2C9 (e.g., phenytoin) substrates.				Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of CYP2C8 and CYP2C9, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX
<b>CYP1A2 Substrates</b>						
Caffeine	HV CT	Single doses 200 mg Caffeine	750 mg BID EPIDIOLEX	Caffeine: 1.15 (1.04, 1.26)	Caffeine: 1.95 (1.62, 2.35)	Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of CYP1A2, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX
<b>CYP2B6 Substrates / Inhibitors</b>						
e.g., bupropion, efavirenz	In vitro	In vitro data predict drug-drug interactions with CYP2B6 substrates (e.g., bupropion, efavirenz), when coadministered with EPIDIOLEX				Because of potential for both induction and inhibition of enzyme activity, consider adjusting dosage of substrates of CYP2B6, as clinically appropriate.
<b>UGT1A7, UGT1A9, and UGT2B7 Substrates / Inhibitors</b>						
e.g., lamotrigine, olanzapine, paracetamol	In vitro	In vitro data predict drug-drug interactions with UGT1A9 substrates (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 substrates (e.g., gemfibrozil, lamotrigine, morphine, lorazepam) when co-administered with EPIDIOLEX.				Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of UGT1A9 and UGT2B7, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX



Co-administered Drug	Source of Evidence	Dose Schedule		Effect on Co-administered Drug Pharmacokinetics		Recommendation
		Co-administered Drug	EPIDIOLEX	C <sub>max</sub> (Geometric mean ratio [90% CI])	AUC (Geometric mean ratio [90% CI])	
<b>P-gp substrates / Inhibitors (orally administered)</b>						
e.g., sirolimus, tacrolimus, digoxin	HV CT	See AEDs, everolimus				

Legend: HV CT = clinical trial with healthy volunteers; Pt CT = clinical trial with patients.

## 9.5 Drug-Food Interactions

Food affects EPIDIOLEX absorption significantly. Both high- and low-fat meals are associated with a marked increase in AUC and C<sub>max</sub>. Bovine milk and alcohol have also been shown to increase the AUC and C<sub>max</sub> of EPIDIOLEX (see [10.3 Pharmacokinetics](#) and [4.4 Administration](#)).

## 9.6 Drug-Herb Interactions

Strong inducers of CYP3A4, such as St. John's wort, when administered concomitantly with CBD, may cause a decrease in the plasma concentrations of CBD and of 7-OH-CBD. These changes may result in a decrease in the effectiveness of CBD. An increase in EPIDIOLEX dosage may be considered (based on clinical response and tolerability).

## 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Advise patients of the potential for positive cannabis drug screens.

# 10 CLINICAL PHARMACOLOGY

## 10.1 Mechanism of Action

The precise mechanisms by which EPIDIOLEX exerts its anticonvulsive effect in humans are unknown. CBD does not exert its anticonvulsive effect through interaction with cannabinoid receptors. CBD reduces neuronal hyperexcitability through modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid cation channel subfamily V member 1 (TRPV1), and modulation of adenosine-mediated signaling through inhibition of adenosine transport via the equilibrative nucleoside transporter-1 (ENT-1). CBD is structurally distinct from other antiepileptic drugs (AEDs).

## 10.2 Pharmacodynamics

### Drug Likability Study

In a human drug likability study, acute administration of EPIDIOLEX to non-dependent adult recreational drug users at therapeutic and suprathreshold doses (750, 1500, and 4500 mg in the fasted state, which is equivalent to 10, 20, and 60 mg/kg in a 75 kg adult), done under fasting conditions, produced small responses on positive subjective measures such as Drug Liking and Take

Drug Again. Compared to dronabinol (10 and 30 mg synthetic  $\Delta^9$ -tetrahydrocannabinol [THC]) and alprazolam (2 mg), EPIDIOLEX has no significant potential for drug taking. However, the drug likability of cannabidiol was likely underestimated in this study because the significant food effect on cannabidiol absorption as high-fat food results in a 5-fold increase in peak concentration and 4-fold increase in exposure.

In a trial specifically designed to test drug withdrawal in healthy adults, the participants took EPIDIOLEX 1500 mg in two doses, 30 minutes before their breakfast or evening meal. EPIDIOLEX produced no signs or symptoms that were associated with a withdrawal syndrome or physical dependence after its abrupt discontinuation after four weeks of stable dosing. However, psychological dependence cannot be ruled out (see [7 General](#) and [8 ADVERSE REACTIONS](#)).

### Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, placebo-controlled, multiple-dose study in 78 healthy adults at a therapeutic dose of 10 mg/kg twice daily to a maximum suprathreshold single dose up to 40 mg/kg under fed conditions. Concentration-dependent QTc prolongation was observed for EPIDIOLEX. At exposures obtained when administered as monotherapy at recommended doses with a high-fat meal, EPIDIOLEX did not prolong the QTc interval greater than 10 msec.

The placebo- and baseline-controlled least squares mean QTc ranged from -5.0 msec (on Day 1 on 10 mg/kg twice daily) to 6.2 msec (on Day 9 on 40 mg/kg once daily), with an indication of dose dependency. The placebo and baseline-controlled PR interval ranged from 0.2 msec to 12.4 msec while the placebo- and baseline controlled QRS was within  $\pm 1.5$  msec. The placebo- and baseline-controlled heart rate ranged from -3.1 (-6.90, 0.66) bpm to 3.2 (-6.3, 7.07) bpm.

Concentration-dependent QTc prolongation was observed with cannabidiol, with a model-predicted prolongation of 4 msec (90% CI 2-6) at a concentration of 1375 ng/mL, which is the predicted peak concentration for the dose of 40 mg/kg.

### **10.3 Pharmacokinetics**

CBD demonstrated an increase in exposure that was less than dose-proportional over the range of 5 to 25 mg/kg/day in patients. No study was conducted to evaluate the extent of lymphatic absorption of cannabidiol, particularly under fed conditions. The data from the studies with food is consistent with the available literature to indicate that absorption via the lymphatic route is significant.

#### **Absorption:**

CBD has a time to maximum plasma concentration ( $T_{max}$ ) of 2.5 to 5 hours at steady state ( $C_{ss}$ ).

#### *Effect of Food*

Coadministration of EPIDIOLEX (750 mg) with a high-fat/high-calorie meal increased  $C_{max}$  by 5-fold, AUC by 4-fold, and reduced the total variability, 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 EPIDIOLEX with bovine milk enhanced exposure by approximately 3-fold for  $C_{max}$  and 2.5-fold for AUC. Taking EPIDIOLEX with alcohol also caused enhanced exposure to CBD, with a 63% greater AUC.

**Distribution:**

The apparent volume of distribution in healthy volunteers was 20963 L to 42849 L. Protein binding of the CBD and its metabolites was >94% *in vitro*.

**Metabolism:**

CBD is metabolized in the liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms.

After repeat dosing, the active metabolite of CBD, 7-OH-CBD, has a 38% lower AUC than the parent drug. The 7-OH-CBD metabolite is converted to 7-carboxy-cannabidiol (7-COOH-CBD), which has an approximately 40-fold higher AUC than the parent drug. Based on 2 preclinical models of generalized seizure in mice, 7-OH-CBD is active in both models, whereas 7-COOH-CBD is only anticonvulsive in one model.

**Elimination:**

The half-life of CBD in plasma was 56 to 61 hours after twice-daily dosing for 7 days in healthy volunteers. Effective half-life estimates ranged from 10 to 17 hours. The plasma clearance of CBD following a single EPIDIOLEX 1500 mg dose (approximately equal to the maximum recommended daily dosage) is 1111 L/h.

EPIDIOLEX is excreted in feces, with minor renal clearance.

**Special Populations and Conditions**

- **Pediatrics:** Safety and efficacy of EPIDIOLEX for the treatment of seizures associated with LGS, DS, or TSC have been established in patients 2 years of age and older. The use of EPIDIOLEX in these indications is supported by adequate and well-controlled studies in patients 2 years of age and older with LGS and DS and in patients 1 year of age and older with TSC (see [14 CLINICAL TRIALS](#)). Safety and efficacy of EPIDIOLEX in pediatric patients below 2 years of age have not been studied.
- **Geriatrics:** Pharmacokinetics of CBD has not been studied in patients ≥65 years of age.
- **Age, Weight, Sex, and Race:** Population pharmacokinetic analyses demonstrated that there were no clinically relevant effects of age, body weight, sex, or race on exposure to CBD.
- **Hepatic Insufficiency:** No effects on the exposures of CBD or metabolite exposures were observed following administration of a single dose of EPIDIOLEX 200 mg in patients with mild (Child-Pugh A) hepatic impairment. Patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment had an approximately 2.5- to 5.2-fold higher AUC, compared with healthy volunteers with normal hepatic function (see [4.2 Recommended Dose and Dosage Adjustment](#) and [7 Hepatic/Biliary/Pancreatic](#)).
- **Renal Insufficiency:** No effects on the  $C_{max}$  or AUC of CBD were observed following administration of a single dose of EPIDIOLEX 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.

## **11 STORAGE, STABILITY AND DISPOSAL**

Store EPIDIOLEX in an upright position at room temperature (15°C to 30°C). Protect from freezing.

Replace cap securely after opening. The cap fits properly in place when the adapter is in place.

Use within 12 weeks of first opening the bottle, then discard any remainder.

Keep out of reach and sight of children.

No special requirements for disposal. Dispose of any unused drug product or waste material in accordance with local requirements.

## **12 SPECIAL HANDLING INSTRUCTIONS**

There are no special handling instructions required.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

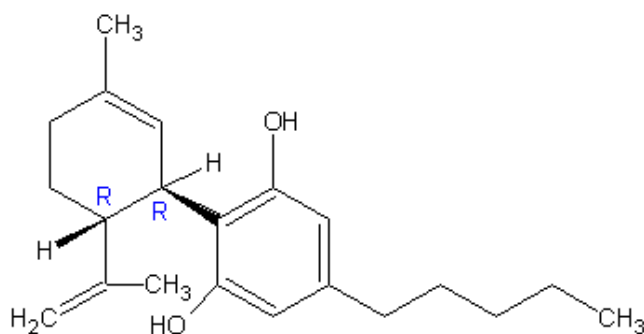
#### Drug Substance

Proper/Common name: cannabidiol

Chemical name: 2-[[1R,6R)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (IUPAC/CAS)

Molecular formula and molecular mass: C<sub>21</sub>H<sub>30</sub>O<sub>2</sub> and 314.46

Structural formula:



Physicochemical properties: Cannabidiol (CBD), the active ingredient in EPIDIOLEX (cannabidiol) oral solution, is a cannabinoid that naturally occurs in the *Cannabis sativa* L. plant. CBD is a white to pale yellow crystalline solid. It is insoluble in water and is soluble in organic solvents. The active pharmaceutical ingredient contains  $\geq 98\%$  cannabidiol with less than 1.5% other cannabinoids including 0.1% or less w/w delta-9-tetrahydrocannabinol.

### 14 CLINICAL TRIALS

#### 14.1 Clinical Trials by Indication

##### Treatment of Seizures associated with Lennox-Gastaut Syndrome

The efficacy of EPIDIOLEX for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) was established in two randomized, double-blind, placebo-controlled trials in patients aged 2 to 47 years.

Study GWPCARE4 compared EPIDIOLEX 20 mg/kg/day with placebo whereas study GWPCARE3 compared EPIDIOLEX doses 10 mg/kg/day and 20 mg/kg/day with placebo. In both studies, patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. Both trials had a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures ( $\geq 2$  drop seizures per week). The baseline period was followed by a 2-week titration period and a 12-week maintenance period. The primary efficacy endpoint in both studies was the percent change (reduction) from baseline in the frequency

(per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over the 14-week treatment period (Titration + Maintenance). Key secondary endpoints in both studies included analyses of change in total seizure frequency and changes from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score at the last visit. For the S/CGIC, the following question was rated on a 7-point scale: “Since [you/your child] started treatment, please assess the status of [you/your child’s] overall condition (comparing [your/their] condition now to [your/their] condition before treatment) using the scale below.” The 7-point scale was as follows: “Very Much Improved” (1); “Much Improved” (2); “Slightly Improved” (3); “No Change” (4); “Slightly Worse” (5); “Much Worse” (6); “Very Much Worse” (7).

In study GWPCARE4, 94% of patients were taking at least 2 concomitant AEDs. The most frequently used concomitant AEDs (>25%) in GWPCARE4 were clobazam (49%), valproate (40%), lamotrigine (37%), levetiracetam (34%), and rufinamide (27%). In GWPCARE3, 94% of patients were taking at least 2 concomitant AEDs. The most frequently used concomitant AEDs (>25%) in GWPCARE3, were clobazam (49%), valproate (38%), levetiracetam (31%), lamotrigine (30%), and rufinamide (29%).

**Table 11: Summary of patient demographics for clinical trials in patients with Lennox-Gastaut Syndrome**

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age	Sex
GWPCARE4 (NCT02224690)	Randomized, double-blind, placebo-controlled study conducted in patients with Lennox-Gastaut syndrome (LGS) who were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet	EPIDIOLEX 20 mg/kg/day or placebo  Oral  4-week baseline period, followed by a 2-week titration period and a 12-week maintenance period	Placebo (n=85) CBD-OS 20 (n=86)	Mean (range): 15 years (2 to 45 years)  Age Groups (n [%])  2-17 years: 113 (66.1%)  18-55 years: 58 (33.9%)	Male: 51%  Female: 49%
GWPCARE3 (NCT02224560)		EPIDIOLEX 10 mg/kg/day dose, 20 mg/kg/day dose or placebo  Oral  4-week baseline period, followed by a 2-week titration period and a 12-week maintenance period	Placebo (n=76) CBD-OS 10 (n=73) CBD-OS 20 (n=76)	Mean (range): 15 years (2 to 47 years)  Age Groups (n [%])  2-17 years: 158 (70.2%)  18-55 years: 67 (29.8%)	Male: 57%  Female: 43%

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age	Sex

In both studies, the median percent change (reduction) from baseline in the frequency of drop seizures was significantly greater in both EPIDIOLEX arms versus placebo ([Table 12](#)).

The results of key secondary endpoints were supportive of the primary endpoint.

**Table 12: Change in Drop Seizure Frequency per 28 days in Lennox-Gastaut Syndrome during the Treatment Period in studies GWPCARE4 and GWPCARE3.**

Drop Seizure Frequency (per 28 Days)	AEDs + EPIDIOLEX 10 mg/kg/day	AEDs + EPIDIOLEX 20 mg/kg/day	AEDs + Placebo
<b>GWPCARE4</b>	—	N=86	N=85
Baseline Period Median Seizure Frequency	—	71	75
Median Percentage Change During Treatment	—	-44	-22
p-value compared to placebo <sup>a</sup>	—	0.01	
<b>GWPCARE3</b>	N=73	N=76	N=76
Baseline Period Median Seizure Frequency	87	86	80
Median Percentage Change During Treatment	-37	-42	-17
p-value compared to placebo <sup>a</sup>	<0.01	<0.01	

<sup>a</sup>Obtained from a Wilcoxon rank-sum test

In GWPCARE4, improvements in the Caregiver Global Impression of Change (CGIC) were reported for 58.3% of EPIDIOLEX patients (Placebo: 34.1%). In GWPCARE3, improvements in CGIC were reported for 57.3% of 20 mg/kg/day and 65.8% of 10 mg/kg/day EPIDIOLEX patients (Placebo: 44%).

In GWPCARE4, during the maintenance period, drop seizure freedom was reported in 5 of 85 patients (5.9%) patients in the EPIDIOLEX 20 mg/kg/day group compared to 0 of 85 (0%) patients in the placebo group.

In GWPCARE3, during the maintenance period, drop seizure freedom was reported in 5 of 76 patients (7%) patients in the EPIDIOLEX 20 mg/kg/day group, and 3 of 73 patients (4%) patients in the EPIDIOLEX 10 mg/kg/day group and 1 of 76 (1%) patients in the placebo group.

### Treatment of Seizures in Patients with Dravet Syndrome

Study GWPCARE1 Part B compared a dose of EPIDIOLEX 20 mg/kg/day with placebo. Study GWPCARE2 compared EPIDIOLEX 10 mg/kg/day and 20 mg/kg/day to placebo. In both studies, patients had a diagnosis of Dravet syndrome (DS) and were inadequately controlled with at least 1 concomitant AED, with or without vagal nerve stimulation or ketogenic diet. During the 4-week baseline period, patients were required to have at least 4 convulsive seizures (tonic-clonic, tonic, clonic, or atonic seizures) while on stable AED therapy. The baseline period was followed by a 2-week titration period and a 12-week

maintenance period. The primary efficacy endpoint was the percent change (reduction) in seizure frequency of convulsive seizures over the 14-week treatment period compared with baseline. Key secondary endpoints in both studies included analyses of change in total seizure frequency and changes from baseline in the Caregiver Global Impression of Change (CGIC) score at the last visit.

In study GWPCARE1 Part B, 93% of patients were taking at least 2 concomitant AEDs during the trial. The most commonly used concomitant AEDs (>25%) in this study were clobazam (65%), valproate (57%), stiripentol (43%), levetiracetam (28%), and topiramate (26%). The baseline median convulsive seizure frequency was 13 per 28 days for the combined groups. The primary efficacy endpoint was the percent change (reduction) from baseline in the frequency (per 28 days) of convulsive seizures (all countable atonic, tonic, clonic, and tonic-clonic seizures) over the 14-week treatment period (Titration + Maintenance).

In study GWPCARE2, 94% of patients were taking at least 2 concomitant AEDs during the trial. The most commonly used concomitant AEDs (>25%) in this study were valproate (70%), clobazam (64%), stiripentol (36%), and levetiracetam (27%). The baseline median convulsive seizure frequency was 12 per 28 days for the combined groups. The primary efficacy endpoint was the percent change (reduction) in seizure frequency of convulsive seizures over the 14-week treatment period compared with baseline.

**Table 13: Summary of patient demographics for clinical trials in patients with Dravet Syndrome**

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age	Sex
GWPCARE1 Part B (NCT02091375)	Randomized, double-blind, placebo-controlled study conducted in patients with Dravet syndrome (DS) who inadequately controlled with at least 1 concomitant ASM, with or without vagal nerve stimulation or ketogenic diet	EPIDIOLEX 20 mg/kg/day or placebo  Oral  4-week baseline period, followed by a 2-week titration period and a 12-week maintenance period	Placebo (n=59) CBD-OS 20 (n=61)	Mean (range):  9 years (2 to 18 years)	Male: 52%  Female: 48%
GWPCARE2 (NCT02224703)		EPIDIOLEX 10 mg/kg/day dose, 20 mg/kg/day dose or placebo  Oral  4-week baseline period, followed by a 2-week titration period and a 12-	Placebo (n=65) CBD-OS 10 (n=64) CBD-OS 20 (n=69)	9 years (2 to 18 years)	Male: 47%  Female: 53%



		week maintenance period			
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Key secondary endpoints in both studies included analyses of change in total seizure frequency and changes from baseline in the Caregiver Global Impression of Change (CGIC) score at the last visit.

In the two studies, the percent change (reduction) from baseline in the frequency of convulsive seizures was significantly greater for both EPIDIOLEX arms versus placebo (Table 14).

The results of key secondary endpoints were supportive of the primary endpoint.

**Table 14: Change in Convulsive Seizure Frequency per 28 days in patients with Dravet Syndrome during the Treatment Period in Studies GWPCARE1 Part B and GWPCARE2**

Total Convulsive Seizure Frequency (per 28 Days)	AED + EPIDIOLEX 10 mg/kg/day	AED + EPIDIOLEX 20 mg/kg/day	AED + Placebo
<b>GWPCARE1 Part B</b>	—	<b>N=61</b>	<b>N=59</b>
Baseline Period Median Seizure Frequency	—	12	15
Median Percent Change During Treatment	—	-39	-13
p-value compared to placebo <sup>a</sup>	—	0.01	
<b>GWPCARE2</b>	<b>N=66</b>	<b>N=67</b>	<b>N=65</b>
Baseline Period Median Seizure Frequency	14	9	17
Estimated Mean Percent Change in Seizure Frequency	-49	-46	-27
p-value compared to placebo <sup>b</sup>	0.01	0.03	

<sup>a</sup>Obtained from a Wilcoxon rank-sum test

<sup>b</sup> Estimated from a negative binomial regression analysis.

In GWPCARE1 Part B, convulsive seizure freedom during the maintenance period was reported in 7 of 60 (11.7%) DS patients treated with CBD EPIDIOLEX 20 mg/kg/day and 0 of 59 (0%) placebo patients who completed the trial.

In GWPCARE2, convulsive seizure freedom during the maintenance period was reported in 4 of 63 patients (6.3%) patients in the EPIDIOLEX 20 mg/kg/day group, and 2 of 66 patients (3.0%) patients in the EPIDIOLEX 10 mg/kg/day group and 1 of 65 (1.5%) patients in the placebo group.

In GWPCARE1 Part B, improvements in the Caregiver Global Impression of Change were reported for 61.7% of EPIDIOLEX 20 mg/kg/day patients (Placebo: 34.5%). In GWPCARE2, improvements in the Caregiver Global Impression of Change were reported for 60.6% of 20 mg/kg/day and 68.2% of 10 mg/kg/day EPIDIOLEX patients (Placebo: 41.5%).

### Treatment of Seizures in Patients with Tuberous Sclerosis Complex

Study GWPCARE6 compared EPIDIOLEX 25 and 50 mg/kg/day with placebo. Patients had a diagnosis of tuberous sclerosis complex (TSC) and their seizures were inadequately controlled with at least one concomitant AED, with or without vagal nerve stimulation or ketogenic diet. During the 4-week baseline period, patients had at least 8 seizures (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]), with a minimum of 1 seizure occurring in at least 3 of the 4 weeks. The baseline period was followed by a 4-week titration period and a 12-week maintenance period.

In this study, all patients but 1 (in EPIDIOLEX 25 mg/kg/day group) were taking 1-5 concomitant AEDs during the trial. The most commonly used concomitant AEDs (>25%) were valproate (45%), vigabatrin (33%), levetiracetam (29%), and clobazam (27%). The baseline median TSC-associated seizure frequency was 57 per 28 days for the combined groups. The primary efficacy endpoint was the percent change (reduction) in seizure frequency of TSC-associated seizures over the 16-week treatment period (Titration + Maintenance) compared with baseline.

**Table 15: Summary of patient demographics for clinical trials in Tuberous Sclerosis Complex**

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age	Sex
GWPCARE6 (NCT02544763)	Randomized, double-blind, placebo-controlled study conducted in patients with seizures associated with tuberous sclerosis complex who are inadequately controlled with at least one concomitant AED, with or without vagal nerve stimulation or ketogenic diet	EPIDIOLEX 25 mg/kg/day dose, 50 mg/kg/day dose or placebo  Oral  4-week baseline period, followed by a 4-week titration period and a 12-week maintenance period	Placebo (n=76) CBD-OS 25 mg (n=75) CBO-OS 50 (n=73)	Mean (range): 14 years (1 to 56 years)  Age Groups (n [%])  1-17 years: 166 (74.1%)  18-65 years: 58 (25.9%)	Male: 58%  Female: 42%

Results show that the mean percent change (reduction) from baseline in the frequency of TSC-associated seizures was significantly greater for patients treated with EPIDIOLEX than for placebo (Table 16).

**Table 16: Change in TSC-associated Seizure Frequency during the Treatment Period in study GWPCARE6**

Total TSC-associated Seizure Frequency (per 28 Days)	EPIDIOLEX 25 mg/kg/day	Placebo
<b>GWPCARE6</b>	N=75	N=76
Baseline Period Seizure Frequency	56	54
Estimated Mean Percent Change in Seizure Frequency	-49	-27
p-value compared to placebo <sup>a</sup>	0.0009	

TSC = tuberous sclerosis complex.

<sup>a</sup> Estimated from a negative binomial regression analysis.

In GWPCARE6, 4 of 71 patients (6%) treated with EPIDIOLEX 25 mg/kg/day reported no TSC-associated seizures (Placebo: 0%).

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

**General toxicology:** Oral administration of CBD (0, 15, 50 or 150 mg/kg/day) to rats for 26 weeks followed by a 4 week off-dose recovery period resulted in changes in animals administered  $\geq$  50 mg/kg/day, including: liver centrilobular hypertrophy, thyroid hypertrophy in both sexes, increased adrenocortical vacuolation in males, pale foci in lungs and increases in pulmonary foamy macrophages. None of these changes were adverse and all showed reversibility. The plasma exposure at 50 mg/kg/day corresponds to approximately 14 and 8 times that of the highest recommended human doses (RHD) of 20 and 25 mg/kg/day, respectively, for Dravet syndrome and Lennox-Gastaut syndrome or tuberous sclerosis complex, respectively.

Oral administration of CBD (0, 100, 150 or 300 mg/kg/day) to mice for 13 weeks resulted in liver centrilobular hypertrophy in some animals given 100 or 150 mg/kg/day and in all animals given 300 mg/kg/day. This resulted in plasma exposures at 100 mg/kg/day of approximately 8 and 4 times that of the highest RHDs of 20 and 25 mg/kg/day, respectively.

Oral administration of CBD (0, 10, 50 or 100 mg/kg/day) to dogs for 39 weeks with a 4 week off-dose recovery period resulted in hepatocyte hypertrophy at doses greater than 10 mg/kg/day and was associated with increased liver weights. This resulted in plasma exposures of approximately 5 and 3 times that of the highest RHDs of 20 and 25 mg/kg/day, respectively.

At this time, the effect of the CBD metabolite, 7-COOH-CBD, is being assessed in repeat-dose toxicology studies.

**Genotoxicity:** CBD was negative for genotoxicity in *in vitro* (Ames) and *in vivo* (rat Comet and bone marrow micronucleus) assays. The CBD metabolites, 7-OH-CBD and 7-COOH-CBD, were negative for genotoxicity *in vitro* (Ames). 7-COOH-CBD is currently being assessed in *in vivo* (rat Comet and bone marrow micronucleus assays) and 7-OH-CBD is currently being assessed in *in vitro* (Mammalian chromosome aberration test).

**Carcinogenicity:** In a carcinogenicity study in mice, oral administration of CBD (0 [water], 0 [vehicle], 30, 100, or 300 mg/kg/day) for 2 years resulted in an increased incidence of hepatocellular adenomas in male mice at all doses tested and in female mice at the highest dose tested. At the high dose (300 mg/kg/day), plasma exposures (AUC) were approximately 12 and 7 times that at the RHDs of 20 and 25 mg/kg/day, respectively, corresponding to maximum recommended doses for Dravet and Lennox-Gastaut syndrome or tuberous sclerosis complex, respectively.

Studies on the effect of CBD and the CBD metabolite 7-COOH-CBD in rats on carcinogenic potential are ongoing.

**Reproductive and Developmental Toxicology:** Oral administration of CBD (0, 75, 150, or 250 mg/kg/day) to pregnant rats throughout the period of organogenesis resulted in embryofetal mortality at the highest dose tested. Aside from slight differences in body weight gain, there were no other drug-related maternal or developmental effects. The highest no-effect dose for embryofetal toxicity in rats was associated with maternal plasma CBD exposures (AUC) approximately 16 and 9 times that in humans at the RHD) of 20 and 25 mg/kg/day, respectively, corresponding to maximum recommended doses for DS and LGS or TSC, respectively.

Oral administration of CBD (0, 50, 80, or 125 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in decreased fetal body weights and increased fetal structural variations at the highest dose tested, which was also associated with maternal toxicity. Maternal plasma CBD exposures at the no-effect level for embryofetal developmental toxicity in rabbits were less than that in humans at the RHDs.

When CBD (75, 150, or 250 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, decreased growth, delayed sexual maturation, neurobehavioral 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 greater or equal to 150 mg/kg. These effects occurred in the absence of maternal toxicity. The no-effect dose for pre- and post-natal developmental toxicity in rats was associated with maternal plasma CBD exposures approximately 9 and 5 times that in humans at the RHDs of 20 and 25 mg/kg/day, respectively.

Oral administration of CBD (0, 75, 150, or 250 mg/kg/day) to male and female rats, prior to and throughout mating and continuing in females during early gestation, produced no adverse effects on mating or fertility. No changes were noted in effects on male or female reproductive indices, male reproductive organ weights, or female estrus cycling. The highest dose tested was associated with plasma exposures approximately 34 times that in humans at a dosage of 25 mg/kg/day.

Studies on the effect of the CBD metabolite, 7-COOH-CBD in reproductive and developmental toxicity are ongoing.

**Juvenile Toxicity:** Administration of CBD (subcutaneous doses of 0 or 15 mg/kg on Postnatal Days (PNDs) 4 to 6 followed by oral administration of 0, 100, 150, or 250 mg/kg on PNDs 7 to 77) to juvenile rats for 10 weeks resulted in increased body weight, delayed male sexual maturation, neurobehavioral effects (decreased locomotor activity and auditory startle habituation), 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 subcutaneous/100 oral mg/kg) was associated with CBD exposures (AUC) approximately 15 and 8 times that in humans at the recommended human doses of 20 and 25 mg/kg/day, respectively, corresponding to maximum recommended doses for DS and LGS, or TSC, respectively.

Studies on the effect of the CBD metabolite, 7-COOH-CBD, in juvenile toxicity are ongoing.

**Re-enforcing Property:** Animal studies of the re-enforcing properties of cannabidiol show that cannabidiol does not produce cannabinoid-like behavioral responses, including generalization 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.

## **PATIENT MEDICATION INFORMATION**

### **READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrEPIDIOLEX®**

#### **Cannabidiol oral solution**

Read this carefully before you start taking **EPIDIOLEX** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EPIDIOLEX**.

#### **What is EPIDIOLEX used for?**

EPIDIOLEX is used in combination with other medicines used to treat seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 2 years of age and older.

#### **How does EPIDIOLEX work?**

The way that EPIDIOLEX works is not fully understood. However, it is thought that EPIDIOLEX works by lowering the excitability of the brain cells that cause seizures.

#### **What are the ingredients in EPIDIOLEX?**

Medicinal ingredient: cannabidiol

Non-medicinal ingredients: anhydrous alcohol, sesame seed oil, strawberry flavouring, and sucralose

#### **EPIDIOLEX comes in the following dosage forms:**

Oral solution: 100 mg/mL

#### **Do not use EPIDIOLEX if:**

- you are allergic to EPIDIOLEX or any of its ingredients.
- if your healthcare professional determines that you have certain abnormal liver blood tests.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EPIDIOLEX. Talk about any health conditions or problems you may have, including if you:**

- have liver problems.
- have or had depression or have tried to harm yourself.
- are pregnant, think you are pregnant, or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if EPIDIOLEX passes into your breast milk.

#### **Other warnings you should know about:**

**Pregnancy:** EPIDIOLEX may harm your unborn baby. Only take EPIDIOLEX during pregnancy if you and your healthcare professional have discussed the risks and have decided that you should. If you become pregnant while taking EPIDIOLEX, talk to your healthcare professional about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicines

during pregnancy. Information on the registry can also be found at the following website:  
<http://www.aedpregnancyregistry.org/>.

**Fertility:** If you are a woman of child-bearing potential or a fertile man, use reliable contraception during your treatment with EPIDIOLEX.

**Driving and using machines:** EPIDIOLEX can make you feel sleepy. Avoid driving and using machinery until you know how EPIDIOLEX affects you.

**Monitoring and Tests:** Your healthcare professional may perform tests before you start treatment with EPIDIOLEX and while you are taking it. Your healthcare professional may monitor:

- your liver function and enzyme levels.
- your mood and behaviour.

**Tell your healthcare professional if you are planning to have a cannabis drug test.** EPIDIOLEX may affect your test results. Tell the person giving the drug test that you are taking EPIDIOLEX.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with EPIDIOLEX:**

- Alcohol may increase sleepiness.
- Caffeine may increase the effects of EPIDIOLEX.
- Other medicines used to treat seizures, such as carbamazepine, clobazam, lamotrigine, lorazepam, phenytoin, stiripentol and valproate.
- Medicines used to treat bacterial infections, such as rifampin, clarithromycin, and erythromycin.
- Other medicines used to treat tuberous sclerosis complex including everolimus.
- Medicines used to treat acid reflux (heartburn or acid regurgitation) such as omeprazole.
- Medicines used in the treatment of anxiety, such as diazepam and clobazam.
- St. John's wort (*Hypericum perforatum*) (a herbal medicine that may be used to treat mild depression or mild anxiety).

EPIDIOLEX may interact with many other medicines. If you are unsure about any of the medicines you take, talk to your healthcare professional.

**How to take EPIDIOLEX:**

- Read the “**Instructions for the Oral Use of EPIDIOLEX**” below for detailed instructions on how to use EPIDIOLEX.
- Take EPIDIOLEX exactly as your healthcare professional tells you to.
- EPIDIOLEX can be taken with or without food, but you should try to take it the same way each day (either with food, or without food), so you get the same effect each time.
  - If you take EPIDIOLEX with food, try to take it with a similar meal type each time (e.g., a meal with a similar fat content).
- Do NOT stop taking EPIDIOLEX suddenly, as this can increase the number of seizures you have and their severity. If you want to stop your treatment, talk to your healthcare professional first.
- If necessary, EPIDIOLEX may be taken via a nasogastric or gastrostomy tube. Your healthcare professional will give you directions on how to do this. Check with your healthcare professional if you are not sure.

**Usual dose:**

Your healthcare professional will tell you how much EPIDIOLEX to take each day, when to take it and which syringe you should use for your dose (1 mL or 5 mL).

The dose is calculated according to your body weight. You may start on a low dose that your healthcare professional gradually increases over time. If you have any questions about your dose, talk to your healthcare professional.

**Instructions for the Oral Use of EPIDIOLEX:****Important:**

- Follow your healthcare professional's instructions for the dose of EPIDIOLEX to take or give.
- Ask your healthcare professional if you are not sure how to prepare, take, or give the prescribed dose of EPIDIOLEX.
- Always use the oral syringe provided with EPIDIOLEX to make sure you measure the right amount of EPIDIOLEX.
- Do not use EPIDIOLEX after the expiration date on the package and each bottle.
- Use EPIDIOLEX within 12 weeks of first opening the bottle.
- After 12 weeks, safely dispose of any EPIDIOLEX that has not been used.

**Each package contains:**

Child-resistant cap



2 bottle adapters (1 bottle adapter for the 1 mL syringe and 1 bottle adapter for the 5 mL syringe)

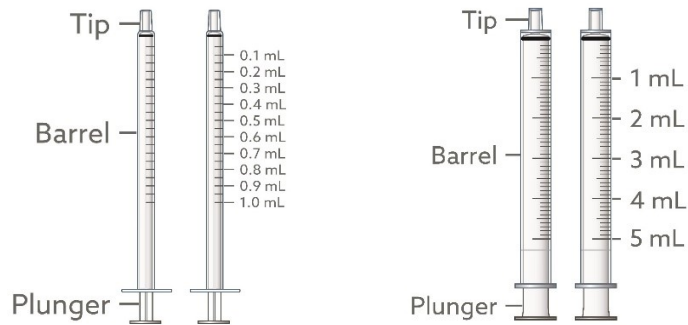


1 bottle of EPIDIOLEX oral solution (100 mg/mL)





**2 reusable 1 mL oral syringes and 2 reusable 5 mL oral syringes:**



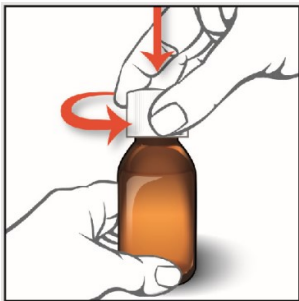
For each syringe size:

- 1 syringe to take or give the dose of EPIDIOLEX
- 1 extra syringe (included as a spare if needed)

Note: If you lose or damage an oral syringe, or cannot read the markings, use the spare syringe.

**Prepare The Bottle - to use EPIDIOLEX for the first time**

1. Remove the child-resistant cap by pushing down while turning the cap to the left (counter-clockwise).



2. Push the appropriate bottle adapter firmly into the bottle.

**Dose**

1 mL or less

More than 1 mL

**Bottle adapter and syringe**

Use the 1 mL bottle adapter and oral syringe

Use the 5 mL bottle adapter and oral syringe

**Make sure the bottle adapter is fully inserted.** If not fully inserted, small parts such as the bottle adapter may become a choking hazard for children and pets.

Note: **Do not** remove the bottle adapter from the bottle after it is inserted.



**Prepare The Dose**

Your healthcare provider will tell you how much EPIDIOLEX to take or give.

3. Use this table to measure the total dose of EPIDIOLEX.

**Dose**

1 mL or less

More than 1 mL and less than 5 mL

More than 5 mL

**How to measure**

Use the 1 mL oral syringe **1 time**

Use the 5 mL oral syringe **1 time**

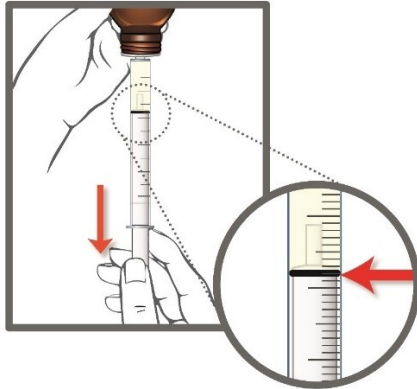
Use the 5 mL oral syringe more than 1 time

4. Push the plunger all the way down and insert the tip of the oral syringe fully into the bottle adapter. With the oral syringe in place, turn the bottle upside down.



5. Slowly pull the plunger of the oral syringe to withdraw the dose of EPIDIOLEX needed.

**Line up** the end of the plunger with the marking for your dose of EPIDIOLEX.



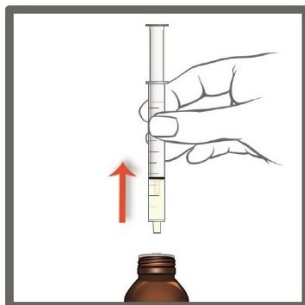
**What to do if you see air bubbles:**

If there are air bubbles in the oral syringe, keep the bottle upside down and push the plunger so that all of the liquid flows back into the bottle. Repeat **Step 5** until the air bubbles are gone.

6. When you have measured the correct dose of EPIDIOLEX, leave the oral syringe in the bottle adapter and turn the bottle right side up.

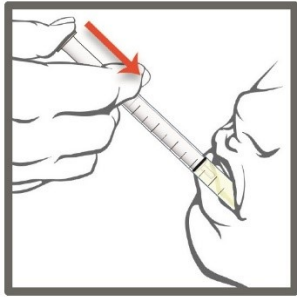


7. Carefully remove the oral syringe from the bottle adapter.



## Give EPIDIOLEX

- Place the tip of the oral syringe against the inside of the cheek and gently push the plunger until all the EPIDIOLEX in the syringe is given.



**Do not** forcefully push on the plunger.

**Do not** direct the medicine to the back of the mouth or throat. This may cause choking.

**If the dose of EPIDIOLEX prescribed by the healthcare provider is more than 5 mL,** repeat steps 4 through 8 to complete the dose.

For example:

If your dose of EPIDIOLEX is 8 mL, withdraw 5 mL of medicine into the syringe and give the medicine. Insert the tip of the oral syringe back into the bottle adapter and withdraw 3 mL of medicine. Give the medicine to receive a total dose of 8 mL.

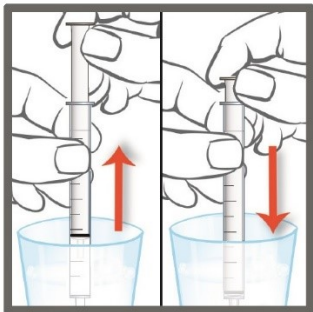
## Clean Up

- Screw the child-resistant cap back on the bottle tightly by turning the cap to the right (clockwise).

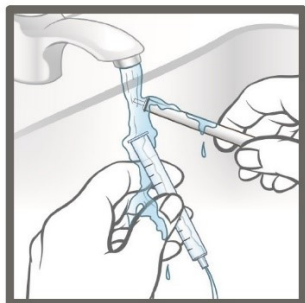


**Do not** remove the bottle adapter. The cap will fit over it.

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

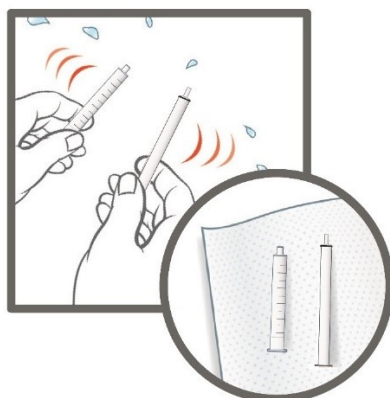


11. Remove the plunger from the barrel of the oral syringe and rinse both parts under tap water.



**Do not** wash the oral syringe in the dishwasher.

12. Shake off any extra water from the plunger and oral syringe barrel and **allow them to air dry until next use.**



**Make sure** the oral syringe is completely dry before the next use.

If water is inside the syringe, it could cause the oil-based medicine to look cloudy. This does not change the safety or how well the medicine works. Continue to use the cloudy liquid as prescribed by your healthcare provider.

If the oral syringe is not completely dry, use the spare syringe provided in the pack.

**Do not throw away the oral syringe.**

#### **Overdose:**

If you think you, or a person you are caring for, have taken too much EPIDIOLEX, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

#### **Missed Dose:**

If you forget to take a dose, do not take a double dose to make up for a forgotten dose. Skip the missed dose and take the next dose at your regular time. If you miss more than 7 days of doses, please talk to your healthcare professional about the correct dose to take.

#### **What are possible side effects from using EPIDIOLEX?**

These are not all the possible side effects you may have when taking EPIDIOLEX. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- diarrhea
- tiredness or loss of energy
- sleepiness or drowsiness
- decreased appetite
- feeling irritable
- fever
- vomiting
- nausea
- constipation
- cough
- rash
- change in walking or gait

It is **very common** for EPIDIOLEX to cause abnormal liver test results. Your healthcare professional will do blood tests during your treatment to monitor your liver enzyme levels. If you experience dark urine, fatigue, abdominal pain, loss of appetite, or yellowing of the skin or eyes, talk to a healthcare professional **right away**.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
<b>VERY COMMON</b>			
<b>Status epilepticus</b> (a single long-lasting seizure or several shorter seizures that occur without consciousness between seizures)			√
<b>COMMON</b>			
<b>Anemia</b> (decreased number of red blood cells): fatigue, loss of energy, looking pale, shortness of breath, weakness		√	
<b>Eosinophilia</b> (increased number of certain white blood cells): abdominal pain, rash, weight loss, wheezing		√	
<b>Pneumonia</b> (infection in the lungs): chest pain when you breathe or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, nausea, vomiting or diarrhea, shortness of breath		√	
<b>Urinary tract infection</b> (infection in urinary system): pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		√	
Weight loss	√		
<b>NOT KNOWN</b>			
<b>Allergic reaction:</b> rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Thoughts of suicide or hurting yourself		√	
<b>Worsening seizures:</b> seizures happening more often in people who already have epilepsy		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

Store EPIDIOLEX at room temperature (15°C to 30°C).

Always store EPIDIOLEX in an upright position. Protect from freezing.

Keep the child-resistant cap tightly closed.

Use EPIDIOLEX within 12 weeks of first opening the bottle. Dispose of any unused EPIDIOLEX after 12 weeks.

Keep out of reach and sight of children.

### If you want more information about EPIDIOLEX:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website [www.jazzpharma.com](http://www.jazzpharma.com); by calling 1-800-520-5568 or by email to [medinfo-ca@jazzpharma.com](mailto:medinfo-ca@jazzpharma.com).

This leaflet was prepared by GW Research Ltd.

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