**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use EPIDIOLEX® safely and effectively. See full prescribing information for EPIDIOLEX.**

**EPIDIOLEX® (cannabidiol) oral solution**
**Initial U.S. Approval: 2018**

**----------INDICATIONS AND USAGE----------**
EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older (1)

**----------DOSAGE AND ADMINISTRATION----------**
- Obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment. (2.1, 5.1)
- See Full Prescribing Information for titration. (2.2, 2.3)

Seizures Associated with Lennox-Gastaut Syndrome or Dravet Syndrome
- The recommended starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day). After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). (2.2)
- Based on individual clinical response and tolerability, EPIDIOLEX can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day). (2.2)

Seizures Associated with Tuberous Sclerosis Complex
- The recommended starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day). Increase the dose weekly by 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated, to a recommended maintenance dosage of 12.5 mg/kg twice daily (25 mg/kg/day). (2.3)

Patients with Impaired Hepatic Function
- Dosage adjustment is recommended for patients with moderate or severe hepatic impairment. (2.6, 8.6)

**----------DOSAGE FORMS AND STRENGTHS----------**
Oral solution: 100 mg/mL (3)

**----------CONTRAINDICATIONS----------**
Hypersensitivity to cannabidiol or any of the ingredients in EPIDIOLEX (4)

**----------WARNINGS AND PRECAUTIONS----------**
- Hepatic Injury: EPIDIOLEX can cause transaminase elevations. Concomitant use of valproate and higher doses of EPIDIOLEX increase the risk of transaminase elevations. See Full Prescribing Information for serum transaminase and bilirubin monitoring recommendations. (5.1)
- Somnolence and Sedation: Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX. (5.2)
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts. (5.3)
- Hypersensitivity Reactions: Advise patients to seek immediate medical care. Discontinue and do not restart EPIDIOLEX if hypersensitivity occurs. (5.4)
- Withdrawal of Antiepileptic Drugs: EPIDIOLEX should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus. (5.5)

**----------ADVERSE REACTIONS----------**
The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) in patients with Lennox-Gastaut syndrome or Dravet syndrome are: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections. (6.1)

The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) in patients with tuberous sclerosis complex are: diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and vomiting. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals, Inc. at 1-800-520-5568 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**
- Strong inducer of CYP3A4 or CYP2C19: Consider dose increase of EPIDIOLEX. (7.1)
- Consider a dose reduction of substrates of CYP1A2, CYP2C8, UGT1A9, and orally administered P-gp substrates. (7.2)
- A lower starting dose of orally administered everolimus is recommended. (7.2)
- Consider dose modification of CYP2B6 or CYP2C19 substrates. (7.2)

**----------USE IN SPECIFIC POPULATIONS----------**
Pregnancy: Based on animal data, may cause fetal harm. (8.1)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 05/2026**

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**FULL PRESCRIBING INFORMATION: CONTENTS***


**1 INDICATIONS AND USAGE**
**2 DOSAGE AND ADMINISTRATION**
2.1 Assessments Prior to Initiating EPIDIOLEX
2.2 Dosing for Seizures Associated with Lennox-Gastaut Syndrome or Dravet Syndrome
2.3 Dosing for Seizures Associated with Tuberous Sclerosis Complex
2.4 Administration Instructions
2.5 Discontinuation of EPIDIOLEX
2.6 Patients with Hepatic Impairment
**3 DOSAGE FORMS AND STRENGTHS**
**4 CONTRAINDICATIONS**
**5 WARNINGS AND PRECAUTIONS**
5.1 Hepatic Injury
5.2 Somnolence and Sedation
5.3 Suicidal Behavior and Ideation
5.4 Hypersensitivity Reactions
5.5 Withdrawal of Antiepileptic Drugs (AEDs)
**6 ADVERSE REACTIONS**
6.1 Clinical Trials Experience
**7 DRUG INTERACTIONS**
7.1 Effect of Other Drugs on EPIDIOLEX
7.2 Effect of EPIDIOLEX on Other Drugs
7.3 Concomitant Use of EPIDIOLEX and Valproate
7.4 CNS Depressants and Alcohol
**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
**9 DRUG ABUSE AND DEPENDENCE**
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
**11 DESCRIPTION**
**12 CLINICAL PHARMACOLOGY**
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
**13 NONCLINICAL TOXICOLOGY**
13.1 Carcinogenesis and Mutagenesis
**14 CLINICAL STUDIES**
14.1 Lennox-Gastaut Syndrome
14.2 Dravet Syndrome
14.3 Tuberous Sclerosis Complex
**16 HOW SUPPLIED/STORAGE AND HANDLING**
16.1 How Supplied
16.2 Storage and Handling
**17 PATIENT COUNSELING INFORMATION**

* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Assessments Prior to Initiating EPIDIOLEX

Because of the risk of hepatocellular injury, obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment with EPIDIOLEX *[see Warnings and Precautions (5.1)]*.

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

- The starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day).
- After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day).
- Patients who are tolerating EPIDIOLEX at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated. For patients in whom a more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day. Administration of the 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates than the recommended maintenance dosage of 10 mg/kg/day, but with an increase in adverse reactions.

### 2.3 Dosing for Seizures Associated with Tuberous Sclerosis Complex

- The starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day).
- Increase the dose in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated, to a recommended maintenance dosage 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 dosage may be increased no more frequently than every other day.
- The effectiveness of doses lower than 12.5 mg/kg twice daily has not been studied in patients with TSC.

### 2.4 Administration Instructions

Food may affect EPIDIOLEX levels *[see Clinical Pharmacology (12.3)]*. Consistent dosing of EPIDIOLEX with respect to meals is recommended to reduce variability in cannabidiol plasma exposure.
Calibrated measuring devices (1 mL and 5 mL oral syringes) will be provided and are recommended to measure and deliver the prescribed dose accurately *[see How Supplied/Storage and Handling (16.1)]*. 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 FR).

Discard any unused EPIDIOLEX remaining 12 weeks after first opening the bottle *[see How Supplied/Storage and Handling (16.2)]*.

### 2.5 Discontinuation of EPIDIOLEX

When discontinuing EPIDIOLEX, the dose should be decreased gradually. As with most antiepileptic drugs, abrupt discontinuation should be avoided when possible, to minimize the risk of increased seizure frequency and status epilepticus *[see Warnings and Precautions (5.5)]*.

### 2.6 Patients with Hepatic Impairment

Dose adjustment is recommended in patients with moderate (Child-Pugh B) hepatic impairment or severe (Child-Pugh C) hepatic impairment *[see Warnings and Precautions (5.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*. It may be necessary to have slower dose titration in patients with moderate or severe hepatic impairment than in patients without hepatic impairment (see Table 1).

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

**Table 1: Dose Adjustments in Patients with Hepatic Impairment**

| Hepatic Impairment | Starting Dosage | In Patients with LGS or DS | In Patients with TSC |
|---|---|---|---|
| | | Maintenance Dosage Range | Maintenance Dosage |
| **Mild** | 2.5 mg/kg twice daily (5 mg/kg/day) | 5 to 10 mg/kg twice daily (10 to 20 mg/kg/day) | 12.5 mg/kg twice daily (25 mg/kg/day) |
| **Moderate** | 1.25 mg/kg twice daily (2.5 mg/kg/day) | 2.5 to 5 mg/kg twice daily (5 to 10 mg/kg/day) | 6.25 mg/kg twice daily (12.5 mg/kg/day) |
| **Severe** | 0.5 mg/kg twice daily (1 mg/kg/day) | 1 to 2 mg/kg twice daily (2 to 4 mg/kg/day) | 2.5 mg/kg twice daily (5 mg/kg/day) |

## 3 DOSAGE FORMS AND STRENGTHS

Cannabidiol oral solution: 100 mg/mL of a strawberry-flavored, clear, colorless to yellow solution.

## 4 CONTRAINDICATIONS

EPIDIOLEX is contraindicated in patients with a history of hypersensitivity to cannabidiol or any of the ingredients in the product *[see Description (11) and Warnings and Precautions (5.4)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hepatic Injury

EPIDIOLEX can cause dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). In controlled studies for LGS and DS (10 and 20 mg/kg/day dosages) and TSC (25 mg/kg/day), the incidence of ALT elevations above 3 times the upper limit of normal (ULN) was 13% (10 and 20 mg/kg/day dosages) and 12% (25 mg/kg/day dosage) in EPIDIOLEX-treated patients compared with 1% in patients on placebo. Less than 1% of EPIDIOLEX-treated patients had ALT or AST levels greater than 20 times the ULN. There were cases of transaminase elevations associated with hospitalization in patients taking EPIDIOLEX. In clinical trials, serum transaminase elevations typically occurred in the first two months of treatment initiation; however, there were some cases observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate. 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.

In the postmarketing setting, cases of cholestatic or mixed patterns of liver injury (i.e., based on calculated ratio of [ALT/ULN]/[ALP/ULN] less than 2 and between 2-5, respectively) were reported in patients treated with EPIDIOLEX.

Risk Factors for Transaminase Elevation

*Concomitant Valproate and Clobazam*

The majority of ALT elevations in the controlled studies occurred in patients taking concomitant valproate *[see Drug Interactions (7.3)]*. Concomitant use of clobazam also increased the incidence of transaminase elevations, although to a lesser extent than valproate *[see Drug Interactions (7.2)]*. In EPIDIOLEX-treated patients with LGS or DS (10 and 20 mg/kg/day dosages), the incidence of ALT elevations greater than 3 times the ULN was 30% in patients taking both concomitant valproate and clobazam, 21% in patients taking concomitant valproate (without clobazam), 4% in patients taking concomitant clobazam (without valproate), and 3% in patients taking neither drug. In EPIDIOLEX-treated patients with TSC (25 mg/kg/day), the incidence of ALT elevations greater than 3 times the ULN was 20% in patients taking both concomitant valproate and clobazam, 25% in patients taking concomitant valproate (without clobazam), 0% in patients taking concomitant clobazam (without valproate), and 6% in patients taking neither drug.

Consider discontinuation or dose adjustment of valproate or clobazam if liver enzyme elevations occur.

In the postmarketing setting, cases of elevated ammonia levels were reported in some EPIDIOLEX-treated patients who also had transaminase elevations; where data were available, most cases reported concomitant use of valproate, clobazam, or both. Consider discontinuation or dose adjustment of valproate or clobazam if ammonia level elevations occur.

*Dose*

Transaminase elevations are generally dose-related. In patients with DS or LGS (10 and 20 mg/kg/day) or TSC (25 mg/kg/day), ALT elevations greater than 3 times the ULN were reported in 17% and 12% of patients taking EPIDIOLEX 20 or 25 mg/kg/day, respectively, compared with 1% in patients taking EPIDIOLEX 10 mg/kg/day. The risk of ALT elevations was higher (25%) in patients with TSC receiving a dosage above the recommended maintenance dosage of 25 mg/kg/day in Study 4.

*Baseline Transaminase Elevations*

Patients with baseline transaminase levels above the ULN had higher rates of transaminase elevations when taking EPIDIOLEX. In the DS and LGS controlled trials (Studies 1, 2, and 3) in patients taking EPIDIOLEX 20 mg/kg/day, the frequency of treatment-emergent ALT elevations greater than 3 times the ULN was 30% when ALT was above the ULN at baseline, compared to 12% when ALT was within the normal range at baseline. No patients taking EPIDIOLEX 10 mg/kg/day experienced ALT elevations greater than 3 times the ULN when ALT was above the ULN at baseline, compared with 2% of patients in whom ALT was within the normal range at baseline. In the TSC controlled trial (Study 4) in patients taking EPIDIOLEX 25 mg/kg/day, the frequency of treatment-emergent ALT elevations greater than 3 and 5 times the ULN were both 11% when ALT was above the ULN at baseline, compared to 12% and 6%, respectively, when ALT was within the normal range at baseline.

Monitoring

In general, transaminase elevations of greater than 3 times the ULN in the presence of elevated bilirubin without an alternative explanation are an important predictor of severe liver injury. Early identification of elevated 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 above 2 times the ULN, should be evaluated prior to initiation of EPIDIOLEX treatment.

Prior to starting treatment with EPIDIOLEX, obtain serum transaminases (ALT and AST) 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 dosage and addition of or changes in medications that are known to impact the liver. Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes at baseline.

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. Discontinue EPIDIOLEX in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN. Patients with sustained transaminase elevations of greater than 5 times the ULN should also have treatment discontinued. Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes. Consider dosage adjustment of any coadministered medication that is known to affect the liver (e.g., valproate and clobazam).

### 5.2 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 32% in EPIDIOLEX-treated patients (27% and 34% of patients taking EPIDIOLEX 10 or 20 mg/kg/day, respectively), compared with 11% in patients on placebo and was generally dose-related. The rate was higher in patients on concomitant clobazam (46% in EPIDIOLEX-treated patients taking clobazam compared with 16% 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 (25 mg/kg/day), compared with 17% in 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, could 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.

### 5.3 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27863 AED-treated patients was 0.43%, compared to 0.24% among 16029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age

(5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

**Table 2: Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in the Pooled Analysis**

| Indication | Placebo Patients with Events Per 1000 Patients | Drug Patients with Events Per 1000 Patients | Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients | Risk Difference: Additional Drug Patients with Events Per 1000 Patients |
|---|---|---|---|---|
| Epilepsy | 1.0 | 3.4 | 3.5 | 2.4 |
| Psychiatric | 5.7 | 8.5 | 1.5 | 2.9 |
| Other | 1.0 | 1.8 | 1.9 | 0.9 |
| Total | 2.4 | 4.3 | 1.8 | 1.9 |

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing EPIDIOLEX or any other AED must balance the risk of suicidal thoughts or behaviors 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 behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

### 5.4 Hypersensitivity Reactions

EPIDIOLEX can cause hypersensitivity reactions. Some subjects in the EPIDIOLEX clinical trials had pruritus, erythema, and angioedema requiring treatment, including corticosteroids and antihistamines. Patients with known or suspected hypersensitivity to any ingredients of EPIDIOLEX were excluded from the clinical trials. If a patient develops hypersensitivity reactions after treatment with EPIDIOLEX, the drug should be discontinued. EPIDIOLEX is contraindicated in patients with a prior hypersensitivity reaction to cannabidiol or any of the ingredients in the product, which includes sesame seed oil *[see Description (11)]*.

### 5.5 Withdrawal of Antiepileptic Drugs (AEDs)

As with most antiepileptic drugs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus *[see Dosage and Administration (2.5) and Clinical Studies (14)]*. But if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

## 6 ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in labeling:

- Hepatic Injury *[see Warnings and Precautions (5.1)]*
- Somnolence and Sedation *[see Warnings and Precautions (5.2)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*
- Withdrawal of Antiepileptic Drugs *[see Warnings and Precautions (5.5)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled trials in patients with LGS and DS, 689 patients were treated with EPIDIOLEX, including 533 patients treated for more than 6 months, and 391 patients treated for more than 1 year. In controlled and uncontrolled trials in patients with TSC, 223 patients were treated with EPIDIOLEX, including 151 patients treated for more than 6 months, 88 patients treated for more than 1 year, and 15 patients treated for more than 2 years.

In an expanded access program and other compassionate use programs, 271 patients with DS, LGS, or TSC were treated with EPIDIOLEX, including 237 patients treated for more than 6 months, 204 patients treated for more than 1 year, and 140 patients treated for more than 2 years.

Patients with LGS or DS

In placebo-controlled trials of patients with LGS or DS (includes Studies 1, 2, 3, and a Phase 2 controlled study in DS), 323 patients received EPIDIOLEX *[see Clinical Studies (14.1, 14.2)]*. Adverse reactions are presented below; the duration of treatment in these trials was up to 14 weeks. Approximately 46% of patients were female, 83% were Caucasian, and the mean age was 14 years (range 2 to 48 years). All patients were taking other AEDs.

In controlled trials in LGS or DS, the rate of discontinuation as a result of any adverse reaction was 2.7% for patients taking EPIDIOLEX 10 mg/kg/day, 11.8% for patients taking EPIDIOLEX 20 mg/kg/day, and 1.3% for patients on placebo. The most frequent cause of discontinuations was transaminase elevation. Discontinuation for transaminase elevation occurred at an incidence of 1.3% in patients taking EPIDIOLEX 10 mg/kg/day, 5.9% in patients taking EPIDIOLEX 20 mg/kg/day, and 0.4% in patients on placebo. Somnolence, sedation, and lethargy led to discontinuation in 3% of patients taking EPIDIOLEX 20 mg/kg/day compared to 0% of patients taking EPIDIOLEX 10 mg/kg/day or on placebo.

The most common adverse reactions that occurred in EPIDIOLEX-treated patients with LGS or DS (incidence at least 10% and greater than placebo) were somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections.

Table 3 lists the adverse reactions that were reported in at least 3% of EPIDIOLEX-treated patients, and at a rate greater than those on placebo, in the placebo-controlled trials in LGS and DS.

**Table 3: Adverse Reactions in Patients Treated with EPIDIOLEX in Controlled Trials of LGS and DS (Studies 1, 2, and 3)**

| Adverse Reactions | EPIDIOLEX | | Placebo |
|---|---|---|---|
| | 10 mg/kg/day | 20 mg/kg/day | |
| | N=75<br>% | N=238<br>% | N=227<br>% |
| **Hepatic Disorders** | | | |
| Transaminases elevated | 8 | 16 | 3 |
| **Gastrointestinal Disorders** | | | |
| Decreased appetite | 16 | 22 | 5 |
| Diarrhea | 9 | 20 | 9 |
| Weight decreased | 3 | 5 | 1 |
| Gastroenteritis | 0 | 4 | 1 |
| Abdominal pain, discomfort | 3 | 3 | 1 |
| **Nervous System Disorders** | | | |
| Somnolence | 23 | 25 | 8 |
| Fatigue, malaise, asthenia | 11 | 12 | 4 |
| Lethargy | 4 | 8 | 2 |
| Sedation | 3 | 6 | 1 |
| Irritability, agitation | 9 | 5 | 2 |
| Aggression, anger | 3 | 5 | <1 |
| Insomnia, sleep disorder, poor quality sleep | 11 | 5 | 4 |
| Drooling, salivary hypersecretion | 1 | 4 | <1 |
| Gait disturbance | 3 | 2 | <1 |
| **Infections** | | | |
| Infection, all | 41 | 40 | 31 |
| Infection, other | 25 | 21 | 24 |
| Infection, viral | 7 | 11 | 6 |
| Pneumonia | 8 | 5 | 1 |
| Infection, fungal | 1 | 3 | 0 |
| **Other** | | | |
| Rash | 7 | 13 | 3 |
| Hypoxia, respiratory failure | 3 | 3 | 1 |

Adverse reactions were similar across LGS and DS in pediatric and adult patients.

Patients with TSC

In a placebo-controlled trial of patients with TSC (Study 4), 148 patients received EPIDIOLEX *[see Clinical Studies (14.3)]*. 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.

In the controlled trial in TSC, the rate of discontinuation as a result of any adverse reaction was 11% for patients taking EPIDIOLEX 25 mg/kg/day and 3% for patients on placebo. The most frequent cause of discontinuation was rash (5%).

The most common adverse reactions that occurred in EPIDIOLEX-treated patients with TSC (incidence at least 10% at the recommended dosage and greater than placebo) were diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and vomiting.

Table 4 lists the adverse reactions that were reported in at least 3% of EPIDIOLEX-treated patients, and at a rate greater than those on placebo, in the placebo-controlled trial in TSC.

**Table 4: Adverse Reactions in Patients Treated with EPIDIOLEX in Controlled Trial of TSC (Study 4)**

| **Adverse Reactions** | **EPIDIOLEX** | **Placebo** |
|---|---|---|
| | **25 mg/kg/day** | |
| | **N = 75**<br>**%** | **N = 76**<br>**%** |
| **Hematological changes** | | |
| Anemia | 7 | 1 |
| Platelet count decreased | 5 | 1 |
| Eosinophil count increased | 5 | 0 |
| **Hepatic Disorders** | | |
| Transaminases elevated | 25 | 0 |
| **Gastrointestinal Disorders** | | |
| Diarrhea | 31 | 25 |
| Decreased appetite | 20 | 12 |
| Vomiting | 17 | 9 |
| Nausea | 9 | 3 |
| Gastroenteritis | 8 | 7 |
| Weight decreased | 7 | 0 |
| **Nervous System Disorders** | | |
| Somnolence | 13 | 9 |
| Gait disturbance | 9 | 5 |
| Fatigue, malaise, asthenia | 5 | 1 |
| **Infections** | | |
| Ear infection | 8 | 3 |
| Urinary tract infection | 5 | 0 |
| Pneumonia | 4 | 1 |
| **Other** | | |
| Pyrexia | 19 | 8 |
| Rash | 8 | 4 |
| Rhinorrhea | 4 | 0 |

Adverse reactions were similar in pediatric and adult patients with TSC.

Additional Adverse Reactions in Patients with LGS, DS, or TSC

*Decreased Weight*

EPIDIOLEX can cause weight loss. In the controlled trials of patients with LGS or DS (10 and 20 mg/kg/day), based on measured weights, 16% of EPIDIOLEX-treated patients had a decrease in weight of at least 5% from their baseline weight, compared to 8% of patients on placebo. The decrease in weight appeared to be dose-related, with 18% of patients on EPIDIOLEX 20 mg/kg/day experiencing a decrease in weight at least 5%, compared to 9% in patients on EPIDIOLEX 10 mg/kg/day. In the controlled trial of patients with TSC (25 mg/kg/day), 31% of EPIDIOLEX-treated patients had a decrease in weight of at least 5% from their baseline weight, compared to 8% of patients on placebo. In some cases, the decreased weight was reported as an adverse event (see Tables 3 and 4).

*Hematologic Abnormalities*
EPIDIOLEX can cause decreases in hemoglobin and hematocrit. In controlled trials of patients with LGS or DS, the mean decrease in hemoglobin from baseline to end of treatment was -0.42 g/dL in EPIDIOLEX-treated patients receiving 10 or 20 mg/kg/day and -0.03 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of -1.5% in EPIDIOLEX-treated patients, and -0.4% in patients on placebo. In the trial of patients with TSC, the mean decrease in hemoglobin from baseline to end of treatment was -0.37 g/dL in EPIDIOLEX-treated patients receiving 25 mg/kg/day and 0.07 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of -1.2% in EPIDIOLEX-treated patients, and -0.2% in patients on placebo.

There was no effect on red blood cell indices. Thirty percent (30%) of EPIDIOLEX-treated patients with LGS and DS and 38% of EPIDIOLEX-treated patients with TSC developed a new laboratory-defined anemia during the course of the study (defined as a normal hemoglobin concentration at baseline, with a reported value less than the lower limit of normal at a subsequent time point), versus 13% of patients with LGS and DS on placebo and 15% of patients with TSC on placebo.

*Increases in Creatinine*
EPIDIOLEX can cause elevations in serum creatinine. 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. Results of another study in healthy adults demonstrate that the increases in serum creatinine noted with EPIDIOLEX are not due to a reduction in glomerular filtration rate *[see Clinical Pharmacology (12.2)].*

*Increases in Pneumonia with Concomitant Clobazam*
Pneumonia has been observed in controlled trials in patients with LGS and DS more frequently with clobazam (7 of 41 [17%] in patients receiving 10 mg/kg/day EPIDIOLEX, 13 of 125 [10%] in patients receiving 20 mg/kg/day EPIDIOLEX, and 1 of 123 [1%] receiving placebo) than without concomitant clobazam (0% in patients receiving 10 mg/kg/day EPIDIOLEX, 4 of 113 [4%] in patients receiving 20 mg/kg/day EPIDIOLEX, and 1 of 104 [1%] receiving placebo). In the controlled trial in patients with TSC, pneumonia was observed more frequently with concomitant clobazam (3 of 18 [17%] in patients receiving 25 mg/kg/day EPIDIOLEX and 0 of 25 [0%] receiving placebo) than without clobazam (0 of 57 [0%] in patients receiving 25 mg/kg/day EPIDIOLEX and 1 of 51 [2%] receiving placebo).

## 7 DRUG INTERACTIONS

### 7.1 Effect of Other Drugs on EPIDIOLEX

Strong CYP3A4 or CYP2C19 Inducers
Concomitant use with a strong CYP3A4 and CYP2C19 inducer (rifampin 600 mg once daily) decreased cannabidiol and 7-hydroxy-cannabidiol (7-OH-CBD) plasma concentrations by approximately 32% and 63%. The impact of such changes on efficacy of EPIDIOLEX is not known *[see Clinical Pharmacology (12.3)]*. Consider an increase in EPIDIOLEX dosage (based on clinical response and tolerability) up to 2-fold, when concomitantly used with a strong CYP3A4 and/or CYP2C19 inducer.

### 7.2 Effect of EPIDIOLEX on Other Drugs

Antiepileptic Drugs
*Clobazam*
Concomitant use of EPIDIOLEX with clobazam increases plasma concentrations of N-desmethylclobazam, the active metabolite of clobazam *[see Clinical Pharmacology (12.3)],* which may increase the risk of clobazam-related adverse reactions *[see Adverse Reactions (6.1) and Warnings and Precautions (5.1, 5.2)].* Consider a reduction in dosage of clobazam if adverse reactions known to occur with clobazam are experienced when concomitantly used with EPIDIOLEX.

*Stiripentol*
Concomitant use of EPIDIOLEX with stiripentol increases plasma exposures of stiripentol *[see Clinical Pharmacology (12.3)]*. Monitor for stiripentol-related adverse reactions when concomitantly used with EPIDIOLEX.

Orally Administered P-gp Substrates
Concomitant use of EPIDIOLEX with orally administered everolimus results in an approximately 2.5-fold increase in plasma exposures of everolimus *[see Clinical Pharmacology (12.3)]*. When initiating EPIDIOLEX in patients taking everolimus, monitor therapeutic drug levels of everolimus and adjust the dosage accordingly. In patients on a stable dosage of EPIDIOLEX, it is recommended to initiate everolimus at a lower starting dosage and titrate the dose based on therapeutic drug monitoring.

Increases in exposure of other orally administered P-gp substrates (e.g., sirolimus, tacrolimus, digoxin) may be observed when concomitantly used with EPIDIOLEX. Consider therapeutic drug monitoring and dosage reduction of other P-gp substrates when given orally with EPIDIOLEX.

CYP1A2, CYP2B6, CYP2C8, CYP2C19, and UGT1A9 Substrates
*CYP1A2 Substrates*
Cannabidiol is a weak inhibitor of CYP1A2 *[see Clinical Pharmacology (12.3)]*. Increases in exposure of certain CYP1A2 substrates (e.g., theophylline, tizanidine) may be observed when concomitantly used with EPIDIOLEX. Consider dosage reduction of CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions, as clinically appropriate, when concomitantly used with EPIDIOLEX.

*CYP2B6 Substrates*
Cannabidiol is an inducer and inhibitor of CYP2B6 *[see Clinical Pharmacology (12.3)]*. No clinically significant reduction in exposures of CYP2B6 substrates are observed when concomitantly used with EPIDIOLEX at 7.5 mg/kg twice daily. Changes in exposures of CYP2B6 substrates are unknown when concomitantly used with EPIDIOLEX at doses above 7.5 mg/kg twice daily. Consider dosage modification of CYP2B6 substrates, as clinically appropriate, when concomitantly used with EPIDIOLEX at doses above 7.5 mg/kg twice daily.

*CYP2C8 Substrates*
Concomitant use of EPIDIOLEX may cause clinically significant interactions with CYP2C8 substrates. Consider a reduction in dosage of CYP2C8 substrates, as clinically appropriate, if adverse reactions are experienced when concomitantly used with EPIDIOLEX.

*CYP2C19 Substrates*
Cannabidiol is a moderate inhibitor of CYP2C19 *[see Clinical Pharmacology (12.3)]*. Concomitant use of EPIDIOLEX increases plasma concentrations of CYP2C19 substrates and may increase the risk of adverse reactions. Consider a dosage reduction of CYP2C19 substrates, as clinically appropriate, when concomitantly used with EPIDIOLEX.

For CYP2C19 substrates (e.g., clopidogrel) where efficacy is mainly due to their active metabolite(s), concomitant use of EPIDIOLEX may decrease plasma concentration of the active metabolite(s) and may therefore decrease efficacy. Consider a dosage increase of such CYP2C19 substrates, as clinically appropriate, when concomitantly used with EPIDIOLEX.

*UGT1A9 Substrates*
Cannabidiol is an inhibitor of UGT1A9 *[see Clinical Pharmacology (12.3)]*. Increases in exposure of UGT1A9 substrates may be observed when concomitantly used with EPIDIOLEX. Consider a reduction in dosage of UGT1A9 substrates where minimal concentration changes may lead to serious adverse reactions, as clinically appropriate, when concomitantly used with EPIDIOLEX.

### 7.3 Concomitant Use of EPIDIOLEX and Valproate

Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations *[see Warnings and Precautions (5.1)]*. If such elevations occur, consider discontinuation or reduction of EPIDIOLEX and/or concomitant valproate. Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic drugs and EPIDIOLEX.

### 7.4 CNS Depressants and Alcohol

Concomitant use of EPIDIOLEX with other CNS depressants (including alcohol) may increase the risk of sedation and somnolence *[see Warnings and Precautions (5.2)]*.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Surveillance Program and Pregnancy Exposure Registry

There are two programs, an EPIDIOLEX pregnancy surveillance program and an antiepileptic drug (AED) pregnancy exposure registry, that monitor pregnancy outcomes. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in both, by calling the toll free numbers or visiting the websites below:

- EPIDIOLEX Pregnancy Surveillance Program
  - 1-855-272-7158
  - https://www.epidiolexpregnancystudy.com
- North American Antiepileptic Drug (NAAED) Pregnancy Registry
  - 1-888-233-2334
  - https://www.aedpregnancyregistry.org/

Risk Summary

There are no adequate data on the developmental risks associated with the use of EPIDIOLEX in pregnant women. Administration of cannabidiol to pregnant animals produced evidence of developmental toxicity (increased embryofetal mortality in rats and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, long-term neurobehavioral changes, and adverse effects on the reproductive system in rat offspring) at maternal plasma exposures similar to (rabbit) or greater than (rat) that in humans at therapeutic doses *(see Animal Data)*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively. The background risks of major birth defects and miscarriage for the indicated populations are unknown.

Data

*Animal Data*

Oral administration of cannabidiol (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. 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 cannabidiol exposures (AUC) approximately 16 and 13 times that in humans at the maximum recommended human doses (MRHD) of 20 and 25 mg/kg/day, respectively.

Oral administration of the major human cannabidiol metabolite, 7-COOH-CBD (0, 25, 50 or 100 mg/kg/day), to pregnant rats throughout the period of organogenesis resulted in embryofetal malformations and variations at the highest dose tested, which was not maternally toxic. The highest no-effect dose for embryofetal developmental toxicity in rats (50 mg/kg/day) was associated with maternal plasma 7-COOH-CBD exposures (AUC) approximately 5 and 4 times that in humans at the MRHDs of 20 and 25 mg/kg/day cannabidiol, respectively.

Oral administration of cannabidiol (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 cannabidiol exposures at the no-effect level for embryofetal developmental toxicity in rabbits were less than that in humans at both MRHDs.

When cannabidiol (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 the mid and high dose. 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 cannabidiol exposures approximately 9 and 7 times that in humans at the MRHDs of 20 and 25 mg/kg/day, respectively.

Oral administration of 7-COOH-CBD (0, 20, 40, or 75 mg/kg/day) to rats throughout pregnancy and lactation resulted in adverse effects on neurobehavioral function (locomotor activity) in offspring when tested in adulthood at the mid and high doses, and on reproductive function (increased preimplantation loss) in offspring at all doses. The lowest dose tested, a no-effect dose for pre- and postnatal developmental toxicity in rats (20 mg/kg/day), was associated with maternal plasma 7-COOH-CBD exposures approximately 2 times that in humans at both MRHDs of 20 or 25 mg/kg/day cannabidiol.

### 8.2 Lactation

Risk Summary

There are no data on the presence of cannabidiol 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.

### 8.4 Pediatric Use

Safety and effectiveness of EPIDIOLEX for the treatment of seizures associated with LGS, DS, or TSC have been established in patients 1 year 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 Clinical Studies (14.1, 14.2, 14.3)]*.

Safety and effectiveness of EPIDIOLEX in pediatric patients below 1 year of age have not been established.

Juvenile Animal Data

Administration of cannabidiol (subcutaneous doses of 0 or 15 mg/kg on Postnatal Days (PNDs) 4-6 followed by oral administration of 0, 100, 150, or 250 mg/kg on PNDs 7-77) 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 sc/100 po mg/kg) was associated with cannabidiol exposures (AUC) approximately 4 times that in humans at both MRHDs of 20 and 25 mg/kg/day.

Administration of the major human cannabidiol metabolite 7-COOH-CBD (0, 20, 40, or 80 mg/kg/day) to juvenile rats by subcutaneous injection on PNDs 4-6 followed by oral gavage on PNDs 7-77, for a total of 10 weeks, resulted in mortality, ophthalmic abnormalities, and accelerated female sexual maturation at the mid and high doses, and long-term neurobehavioral (increased locomotor activity, decreased auditory startle response habituation and prepulse inhibition, delayed maze learning) and reproductive functional impairment (disrupted estrous cyclicity, decreased sperm concentration and increased abnormal sperm; decreased mating, fertility, and fecundity indices; increased preimplantation loss), decreased brain weight, and decreased bone density at the high dose. The no-effect dose for developmental toxicity in juvenile rats (20 mg/kg/day) was associated with 7-

COOH-CBD exposures (AUC) that were approximately equivalent to that in humans at the MRHDs of 20 and 25 mg/kg/day.

### 8.5 Geriatric Use

Clinical trials of EPIDIOLEX in the treatment of LGS, DS, and TSC did not include a sufficient number of patients aged above 55 years to determine whether or not they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

### 8.6 Hepatic Impairment

Because of an increase in exposure to EPIDIOLEX, dosage adjustments are necessary in patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*. EPIDIOLEX does not require dosage adjustments in patients with mild hepatic impairment.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

EPIDIOLEX is not a controlled substance.

### 9.2 Abuse

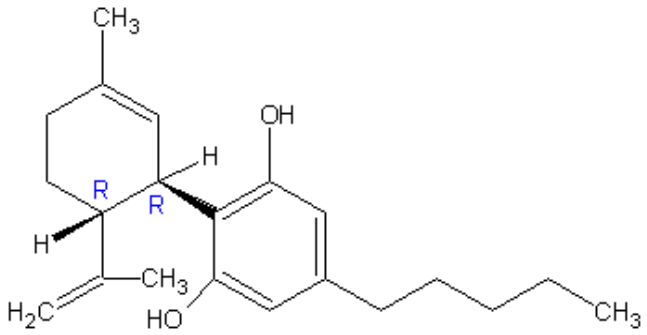
Animal abuse-related studies show that cannabidiol does not produce cannabinoid-like behavioral responses, including generalization to delta-9-tetrahydrocannabinol (THC) in a drug discrimination study. Cannabidiol also does not produce animal self-administration, suggesting it does not produce rewarding effects. In a human abuse potential study, acute administration of cannabidiol to non-dependent adult recreational drug users at therapeutic and supratherapeutic doses of 750, 1500, and 4500 mg in the fasted state (equivalent respectively to 10, 20, and 60 mg/kg in a 75 kg adult) produced responses on positive subjective measures such as Drug Liking and Take Drug Again that were within the acceptable placebo range. In contrast, 10 and 30 mg of dronabinol (synthetic THC) and 2 mg alprazolam produced large increases on positive subjective measures compared to placebo that were statistically significantly greater than those produced by cannabidiol. In other Phase 1 clinical studies conducted with cannabidiol, there were no reports of abuse-related adverse events.

### 9.3 Dependence

In a human physical dependence study, administration of cannabidiol 1500 mg/day (750 mg twice daily) to adults for 28 days did not produce signs or symptoms of withdrawal over a 6-week assessment period beginning three days after drug discontinuation. This suggests that cannabidiol likely does not produce physical dependence.

## 11 DESCRIPTION

Cannabidiol is a cannabinoid designated chemically as 2-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (IUPAC/CAS). Its empirical formula is $C_{21}H_{30}O_2$ and its molecular weight is 314.46. The chemical structure is:




Cannabidiol, the active ingredient in EPIDIOLEX, is a cannabinoid that naturally occurs in the *Cannabis sativa* L. plant.

Cannabidiol is a white to pale yellow crystalline solid. It is insoluble in water and is soluble in organic solvents.

EPIDIOLEX (cannabidiol) oral solution is a clear, colorless to yellow liquid containing cannabidiol at a concentration of 100 mg/mL. Inactive ingredients include dehydrated alcohol (7.9% w/v), sesame seed oil, strawberry flavor, and sucralose. EPIDIOLEX contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The precise mechanisms by which EPIDIOLEX exerts its anticonvulsant effect in humans are unknown. Cannabidiol does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors.

### 12.2 Pharmacodynamics

Cardiac Electrophysiology

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.

Other factors such as food intake, certain concomitant medications (e.g., clobazam), and alcohol consumption may increase the exposure of EPIDIOLEX and the potential effect on QTc prolongation in this scenario is not known.

Effect of EPIDIOLEX on Measured Glomerular Filtration Rate (mGFR)

In a dedicated study in healthy subjects (N=39), EPIDIOLEX (7.5 mg/kg twice daily for 7 days) had no effect on the mGFR and mGFR normalized for body surface area (BSA), as determined by the clearance of probe drug iohexol (5 mL, IV infusion) following EPIDIOLEX administration versus baseline.

In this study, consistent with historic observations *[see Adverse Reactions (6.1)]*, increases in serum creatinine and corresponding decreases in estimated GFR (using a combined serum creatinine- and cystatin C-based estimating equation) and 24-hour urinary creatinine clearance ($CL_{cr}$) of 5% and 10%, respectively, were seen.

The results of this study demonstrate that EPIDIOLEX did not affect mGFR; therefore, the increase in serum creatinine observed with administration of EPIDIOLEX is not due to a reduction in glomerular filtration rate.

### 12.3 Pharmacokinetics

Cannabidiol demonstrated an increase in exposure that was less than dose-proportional over the range of 5 to 25 mg/kg/day in patients.

Absorption

Cannabidiol 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 or 1500 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 subjects *[see Dosage and Administration (2.4)]*. Coadministration of EPIDIOLEX with a low-fat/low-calorie meal increased $C_{max}$ and AUC by 4-fold and 3-fold, respectively. Furthermore, coadministration of EPIDIOLEX with bovine milk increased exposure by approximately 3-fold for $C_{max}$ and 2.5-fold for AUC. Coadministration of EPIDIOLEX with alcohol also caused increased exposure to cannabidiol, with 93% increased $C_{max}$ and 63% greater AUC.

Distribution

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

Elimination

The half-life of cannabidiol in plasma was 56 to 61 hours after twice-daily dosing for 7 days in healthy subjects. The plasma clearance of cannabidiol following a single EPIDIOLEX 1500 mg dose (approximately equal to the 20 mg/kg/day dosage) is 1111 L/h.

*Metabolism*

Cannabidiol 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 cannabidiol, 7-OH-CBD, has a 38% lower AUC than the parent drug. The 7-OH-CBD metabolite is converted to 7-COOH-CBD, which has an approximately 40-fold higher AUC than the parent drug. Based on two mouse models of acute seizure, the 7-OH-CBD metabolite is anticonvulsant in both models and 7-COOH-CBD is anticonvulsant in one model. The relevance of these findings to human epilepsy is unknown.

*Excretion*

EPIDIOLEX is excreted in feces, with minor renal clearance.

Specific Populations

*Patients with Hepatic Impairment*

No effects on the exposures of cannabidiol 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 subjects with normal hepatic function *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), and Use in Specific Populations (8.6)]*.

Drug Interaction Studies

*Clinical Studies and Model-Informed Approaches*

Drug Interaction Studies with AEDs

*Clobazam and Valproate*

The interaction potential with other AEDs (clobazam and valproate) was evaluated in dedicated clinical studies following coadministration of EPIDIOLEX (750 mg twice daily in healthy subjects and 20 mg/kg/day in patients).

Coadministration with clobazam in healthy subjects increased the cannabidiol active metabolite 7-OH-CBD mean $C_{max}$ by 73% and AUC by 47%; and increased the clobazam active metabolite, N-desmethylclobazam, a substrate of CYP2C19, $C_{max}$ and AUC by approximately 3-fold, with no effect on clobazam levels *[see Drug Interactions (7.2)]*.

When EPIDIOLEX was coadministered with valproate in healthy subjects, there was no effect on the systemic exposure to valproate.

In a separate study in epilepsy patients investigating the effect of EPIDIOLEX on valproate exposure, there were decreases in both the plasma $C_{max}$ and AUC of valproate, which were not clinically relevant (approximately 17% and 21%, respectively), and a decrease in exposure of the putative hepatotoxic metabolite of valproate, 2-propyl-4-pentanoic acid (approximately 28% and 33%, respectively).

In healthy subjects, coadministration with valproate resulted in no clinically relevant changes in exposure to cannabidiol or its major metabolites (cannabidiol $C_{max}$ decreased by 26%; 7-OH-CBD AUC increased by 22%; 7-COOH-CBD $C_{max}$ and AUC increased by 25% and 32%, respectively).

*Stiripentol*
When EPIDIOLEX was coadministered with stiripentol in healthy subjects, $C_{max}$ and AUC of stiripentol increased 28% and 55%, respectively. In patients with epilepsy, $C_{max}$ and AUC of stiripentol increased 17% and 30%, respectively *[see Drug Interactions (7.2)]*.

*Everolimus*
Coadministration of EPIDIOLEX (12.5 mg/kg twice daily) with the P-gp and CYP3A4 substrate everolimus (5 mg) in healthy subjects led to an approximately 2.5-fold increase in everolimus mean $C_{max}$ and AUC *[see Drug Interactions (7.2)]*.

Effect of Other Drugs on EPIDIOLEX
*CYP3A4 and CYP2C19 Inhibitors*
Coadministration of EPIDIOLEX with strong inhibitors of CYP3A4 or CYP2C19 had the following effects on exposure to cannabidiol and its metabolites. Itraconazole, a strong CYP3A4 inhibitor, increased exposure by < 10% for cannabidiol and < 20% for 7-OH-CBD and 7-COOH-CBD for both AUC and $C_{max}$. Although the effects of a strong CYP2C19 inhibitor fluconazole were slightly more marked, they are still considered not to be clinically meaningful (cannabidiol increased by 22% and 24% for AUC and $C_{max}$, respectively; 7-OH-CBD decreased by 28% and 41% for AUC and $C_{max}$; 7-COOH-CBD decreased by 33% and 48% for AUC and $C_{max}$).

*CYP3A4 and CYP2C19 Inducers*
Coadministration with rifampin, a strong CYP3A4 and CYP2C19 inducer, caused a decrease in cannabidiol exposure of 32% and 34% for AUC and $C_{max}$ *[see Drug Interactions (7.1)]*. There were larger changes in exposure to the active metabolite (7-OH-CBD decreased by 63% and 67% for AUC and $C_{max}$, 7-COOH-CBD decreased by 48% for AUC, whereas there was no change in $C_{max}$).

Effect of EPIDIOLEX on Other Drugs
*CYP1A2 Substrates*
Coadministration of EPIDIOLEX (750 mg twice daily) with a single dose of caffeine (200 mg), a sensitive CYP1A2 substrate, showed increased caffeine exposure by 15% for $C_{max}$ and 95% for AUC compared to caffeine administered alone *[see Drug Interactions (7.2)]*.

*CYP2B6 Substrates*
Coadministration of EPIDIOLEX (7.5 mg/kg twice daily) with a single dose of bupropion (150 mg), a CYP2B6 substrate, decreased bupropion exposure by 19% for $C_{max}$ and 20% for AUC compared to bupropion administered alone. The $C_{max}$ and AUC of hydroxybupropion, an active metabolite formed by CYP2B6, was not altered. The effect of EPIDIOLEX doses above 7.5 mg/kg twice daily on bupropion and hydroxybupropion is unknown *[see Drug Interactions (7.2)]*.

*CYP2C9 Substrates*
Coadministration of EPIDIOLEX (7.5 mg/kg twice daily) with a single dose of tolbutamide (500 mg), a moderately sensitive CYP2C9 substrate, did not result in changes in plasma exposures of tolbutamide compared to tolbutamide administered alone. No clinically meaningful changes in plasma exposures of tolbutamide were

predicted when tolbutamide is coadministered with steady-state dosing of EPIDIOLEX (12.5 mg/kg twice daily).

*CYP3A4 Substrates*
Coadministration of EPIDIOLEX (750 mg twice daily) with a single dose of midazolam (2.5 mg), a sensitive CYP3A4 substrate, did not result in changes in plasma concentrations of midazolam compared to midazolam administered alone.

*UGT1A9 Substrates*
Coadministration of EPIDIOLEX (7.5 mg/kg twice daily) with a single dose of mycophenolate mofetil (1500 mg) increased mycophenolic acid, a UGT1A9 substrate, exposure by 16% for $C_{max}$ and 35% for AUC when compared to mycophenolate mofetil administered alone. An increase in mycophenolic acid exposure by 9% for $C_{max}$ and 58% for AUC is predicted when mycophenolate mofetil (1500 mg) is coadministered with steady-state dosing of EPIDIOLEX (12.5 mg/kg twice daily) *[see Drug Interactions (7.2)]*.

*UGT2B7 Substrates*
Coadministration of EPIDIOLEX (7.5 mg/kg twice daily) with a single dose of zidovudine (300 mg), a UGT2B7 substrate, increased zidovudine exposure by 7% for $C_{max}$ and 19% for AUC compared to zidovudine administered alone, which is not expected to be clinically significant. No clinically meaningful changes in plasma exposures of zidovudine are predicted when zidovudine is coadministered with steady-state dosing of EPIDIOLEX (12.5 mg/kg twice daily).

*In Vitro Assessment of Drug Interactions*

Drug Metabolizing Enzymes *[see Drug Interactions (7.1, 7.2)]*
Cannabidiol has the potential to inhibit CYP2B6 and CYP2C8, and to induce CYP2B6 at clinically relevant concentrations.

Cannabidiol does not inhibit the uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes UGT1A1, UGT1A3, UGT1A4, UGT1A6, or UGT2B17 isoforms.

Transporters
Cannabidiol and the cannabidiol metabolite, 7-OH-CBD, are not anticipated to interact with BCRP, BSEP, MDR1/P-gp, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, OATP1B1, or OATP1B3. However, due to limitations of the *in vitro* testing procedure, inhibition of P-gp mediated efflux by cannabidiol in the intestine could not be excluded. *In vivo* data show that CBD can affect P-gp efflux activity in the intestine *[see Clinical Studies and Model-Informed Approaches]*.

The cannabidiol metabolite, 7-COOH-CBD, is not a substrate of BCRP, OATP1B1, OATP1B3, or OCT1. However, 7-COOH-CBD is a substrate for P-gp. 7-COOH-CBD is an inhibitor of transport mediated via BCRP and BSEP at clinically relevant concentrations.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis and Mutagenesis

Carcinogenesis
In a carcinogenicity study in mice, oral administration of cannabidiol (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 the highest dose tested. At the mid dose (100 mg/kg/day), plasma exposures (AUC) were approximately 2 and 1 times that at the maximum recommended human doses (MRHDs) of 20 and 25 mg/kg/day, respectively.

In a carcinogenicity study in rats, oral administration of cannabidiol (0 [water], 0 [vehicle], 15, 50, and 150 mg/kg/day) for 2 years, no statistically significant increases in tumor incidences were observed. At the high dose (150 mg/kg/day), the plasma exposures (AUC) were approximately 12.5 and 10 times times that at the MRHDs of 20 and 25 mg/kg/day, respectively.

Mutagenesis

Cannabidiol was negative for genotoxicity in *in vitro* (Ames) and *in vivo* (rat Comet and bone marrow micronucleus) assays. The cannabidiol metabolite 7-COOH-CBD was negative for genotoxicity in in vitro (Ames) and in vivo (rat Comet and bone marrow micronucleus) assays. The metabolite 7-OH-CBD was negative for genotoxicity in in vitro (Ames and mammalian cell [human lymphocyte] chromosomal aberration) assays and in vivo (rat micronucleus) assays.

Impairment of Fertility

Oral administration of cannabidiol (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 fertility. The highest dose tested was associated with plasma exposures (AUC) approximately 18 and 14 times that in humans at the MRHDs of 20 and 25 mg/kg/day, respectively.

## 14 CLINICAL STUDIES

### 14.1 Lennox–Gastaut Syndrome

The effectiveness of EPIDIOLEX for the treatment of seizures associated with LGS was established in two randomized, double-blind, placebo-controlled trials in patients aged 2 to 55 years (Study 1, NCT02224690; and Study 2, NCT02224560).

Study 1 (N=171) compared a dose of EPIDIOLEX 20 mg/kg/day with placebo. Study 2 (N=225) compared a 10 mg/kg/day dose and a 20 mg/kg/day dose of EPIDIOLEX 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 (≥ 2 drop seizures per week). The baseline period was followed by a 2-week titration period and a 12-week maintenance period.

In Study 1, 94% of patients were taking at least 2 concomitant AEDs. The most frequently used concomitant AEDs (greater than 25%) in Study 1 were clobazam (49%), valproate (40%), lamotrigine (37%), levetiracetam (34%), and rufinamide (27%). In Study 2, 94% of patients were taking at least 2 concomitant AEDs. The most frequently used concomitant AEDs (greater than 25%) in Study 2, were clobazam (49%), valproate (38%), levetiracetam (31%), lamotrigine (30%), and rufinamide (29%).

The primary efficacy measure in both studies was the percent change from baseline in the frequency (per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over the 14-week treatment period. 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 [your/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 Studies 1 and 2, the median percent change from baseline (reduction) in the frequency of drop seizures was significantly greater for both dosage groups of EPIDIOLEX than for placebo (Table 5). A reduction in drop seizures was observed within 4 weeks of initiating treatment with EPIDIOLEX, and the effect remained generally consistent over the 14-week treatment period.

**Table 5: Change in Drop Seizure Frequency in Lennox–Gastaut Syndrome during the Treatment Period (Studies 1 and 2)**

| **Drop Seizure Frequency (per 28 Days)** | **Placebo** | **EPIDIOLEX 10 mg/kg/day** | **EPIDIOLEX 20 mg/kg/day** |
|---|---|---|---|
| **Study 1** | **N=85** | **—** | **N=86** |
| Baseline Period Median Seizure Frequency | 75 | — | 71 |
| Median Percentage Change from Baseline During Treatment | −22 | — | −44 |
| p-value compared to placebo[a] | | | 0.01 |
| **Study 2** | **N=76** | **N=73** | **N=76** |
| Baseline Period Median Seizure Frequency | 80 | 87 | 86 |
| Median Percentage Change from Baseline During Treatment | −17 | −37 | −42 |
| p-value compared to placebo[a] | | <0.01 | <0.01 |

[a]Obtained from a Wilcoxon rank-sum test.

Figure 1 displays the percentage of patients by category of reduction from baseline in drop seizure frequency per 28 days during the treatment period in Study 1.

**Figure 1: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Lennox–Gastaut Syndrome (Study 1)**

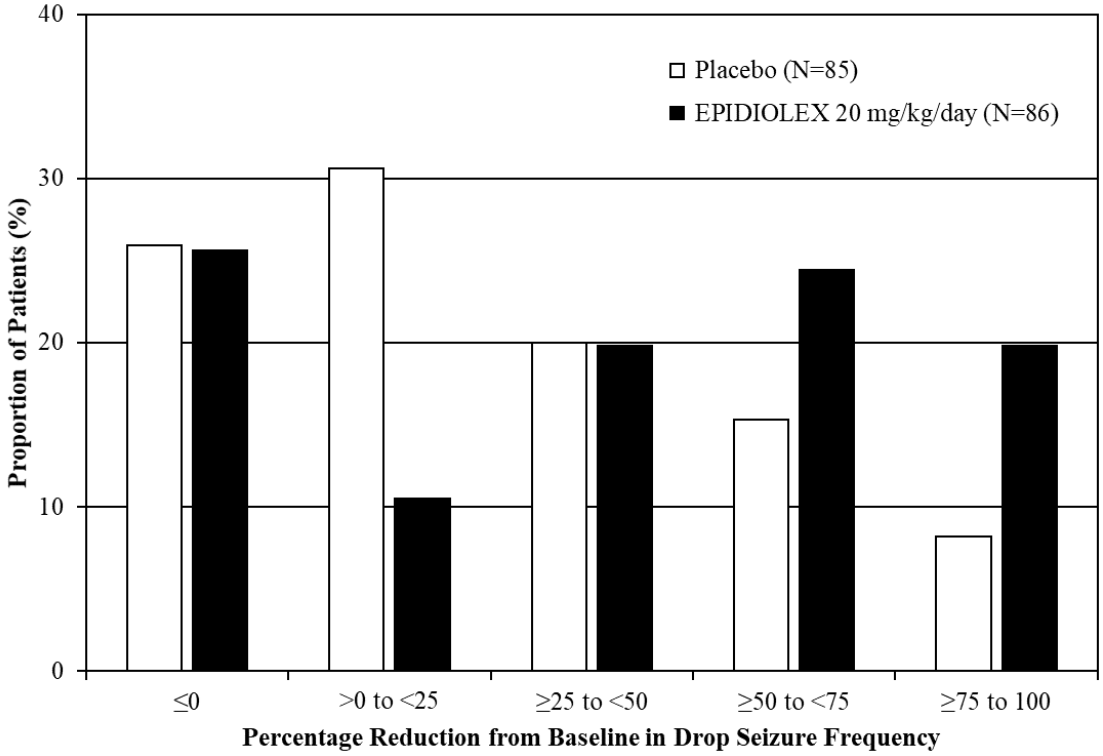
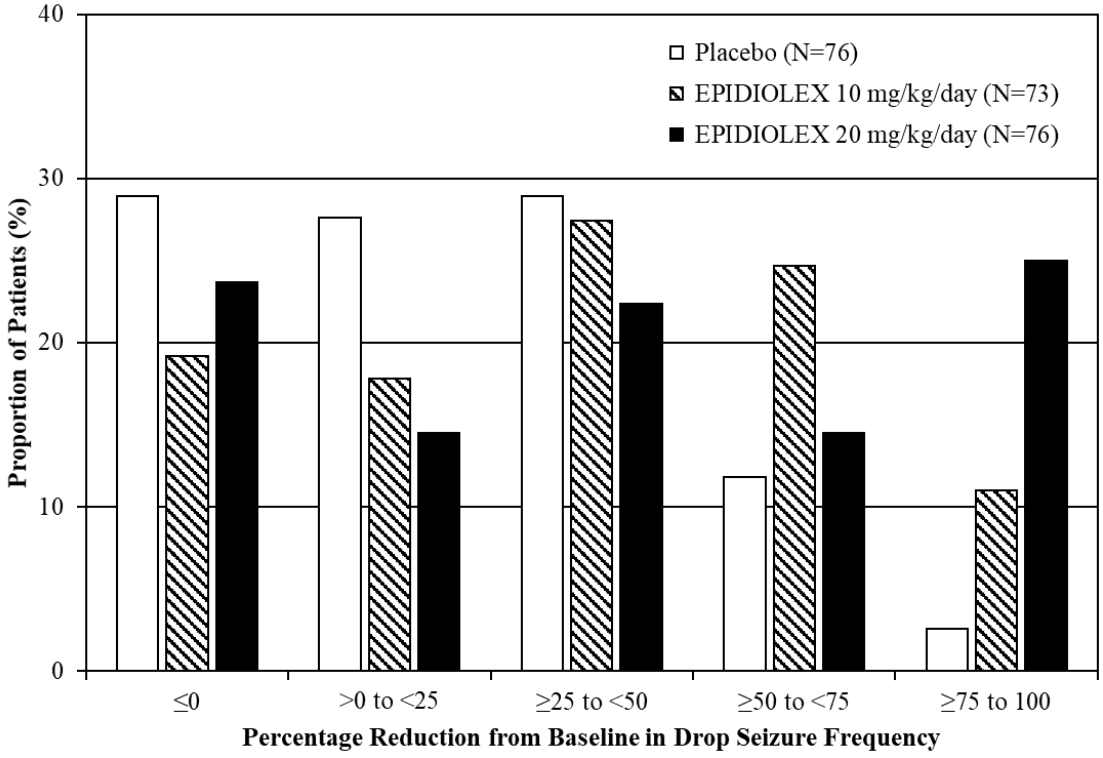



Figure 2 displays the percentage of patients by category of reduction from baseline in drop seizure frequency (per 28 days) during the treatment period in Study 2.

**Figure 2: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Lennox–Gastaut Syndrome (Study 2)**



In Study 1, 3 of 85 (4%) patients in the EPIDIOLEX 20 mg/kg/day group reported no drop seizures during the maintenance period, compared to 0 patients in the placebo group. In Study 2, 3 of 73 (4%) patients in the EPIDIOLEX 10 mg/kg/day group, 5 of 76 (7%) patients in the EPIDIOLEX 20 mg/kg/day group, and 1 of 76 (1%) patients in the placebo group reported no drop seizures during the maintenance period.

In LGS patients, EPIDIOLEX was associated with significant reductions in total seizure frequency (drop and non-drop seizures) versus placebo. During the treatment period in Study 1, the median percent reduction in total seizure frequency (per 28 days) was 41% in patients taking EPIDIOLEX 20 mg/kg/day compared to 14% in patients taking placebo ($p<0.01$). In Study 2, the median percent reduction in total seizure frequency (per 28 days) was 36% in the 10 mg/kg/day group, 38% in the 20 mg/kg/day group, and 18% in the placebo group ($p<0.01$ for both groups).

A greater improvement on the Subject/Caregiver Global Impression of Change (S/CGIC) was reported in patients treated with EPIDIOLEX compared with placebo in Studies 1 and 2. In Study 1, the mean S/CGIC score at last visit was 3.0 in the 20 mg/kg/day EPIDIOLEX group (corresponding to "slightly improved") compared with 3.7 (most closely associated with "no change") in the placebo group ($p<0.01$). In Study 2, the mean S/CGIC score at last visit was 3.0 and 3.2 in the 10 mg/kg/day and 20 mg/kg/day EPIDIOLEX groups, respectively ("slightly improved"), compared with 3.6 ("no change") in the placebo group ($p<0.01$ and $p=0.04$, respectively).

### 14.2 Dravet Syndrome

The effectiveness of EPIDIOLEX for the treatment of seizures associated with DS was demonstrated in a single randomized, double-blind, placebo-controlled trial in 120 patients aged 2 to 18 years (Study 3, NCT02091375). Study 3 compared a dose of EPIDIOLEX 20 mg/kg/day with placebo. Patients had a diagnosis of treatment-resistant DS and 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 were required to have at least 4 convulsive 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 measure was the percent change 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.

In Study 3, 93% of patients were taking at least 2 concomitant AEDs during the trial. The most commonly used concomitant AEDs (greater than 25%) in Study 3 were clobazam (65%), valproate (57%), stiripentol (43%), levetiracetam (28%), and topiramate (26%).

The median percent change from baseline (reduction) in the frequency of convulsive seizures was significantly greater for EPIDIOLEX 20 mg/kg/day than for placebo (Table 6). A reduction in convulsive seizures was observed within 4 weeks of initiating treatment with EPIDIOLEX and the effect remained generally consistent over the 14-week treatment period.

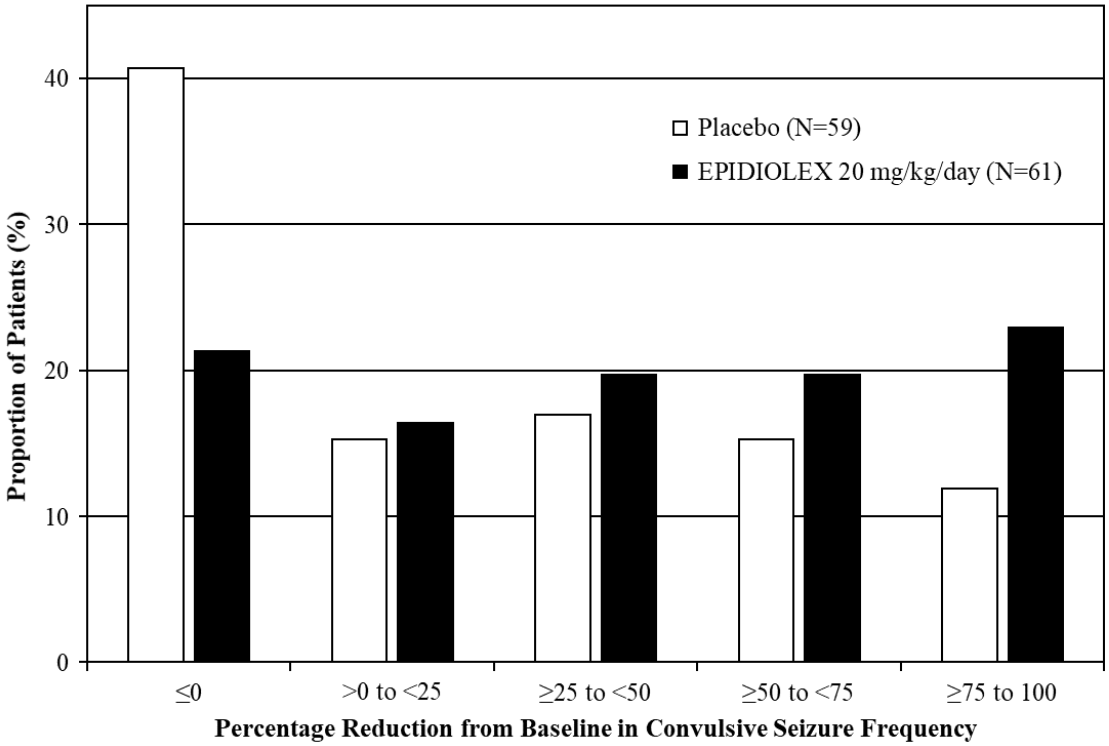
**Table 6: Change in Convulsive Seizure Frequency in Dravet Syndrome during the Treatment Period (Study 3)**

| **Total Convulsive Seizures (per 28 Days)** | **Placebo** | **EPIDIOLEX 20 mg/kg/day** |
|---|---|---|
| **Study 3** | **N=59** | **N=61** |
| Baseline Period Median Seizure Frequency | 15 | 12 |
| Median Percentage Change from Baseline During Treatment | −13 | −39 |
| p-value compared to placebo[a] | | 0.01 |

[a]Obtained from a Wilcoxon rank-sum test.

Figure 3 displays the percentage of patients by category of reduction from baseline in convulsive seizure frequency (per 28 days) during the treatment period in Study 3.

**Figure 3: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Dravet Syndrome (Study 3)**




In Study 3, 4 of 60 (7%) patients treated with EPIDIOLEX 20 mg/kg/day reported no convulsive seizures during the maintenance period, compared to 0 patients in the placebo group.

### 14.3 Tuberous Sclerosis Complex

The effectiveness of EPIDIOLEX for the treatment of seizures associated with TSC was demonstrated in a randomized, double-blind, placebo-controlled trial in 224 patients aged 1 to 65 years (Study 4; NCT02544763).

Study 4 (N=224) compared doses of EPIDIOLEX 25 mg/kg/day and 50 mg/kg/day (2 times the recommended maintenance dosage) with placebo. Patients had a diagnosis of TSC and seizures 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, with at least 1 seizure occurring in at least 3 of the 4 weeks (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]). The baseline period was followed by a 4-week titration period and a 12-week maintenance period.

In Study 4, 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 (greater than 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 measure was the change in seizure frequency of TSC-associated seizures over the 16-week treatment period compared with baseline.

In Study 4, the percentage change from baseline (reduction) in the frequency of TSC-associated seizures was significantly greater for patients treated with EPIDIOLEX than for placebo (Table 7). A reduction in TSC-associated seizures was observed within 4 weeks of initiating treatment with EPIDIOLEX and the effect remained generally consistent over the 12-week maintenance period.

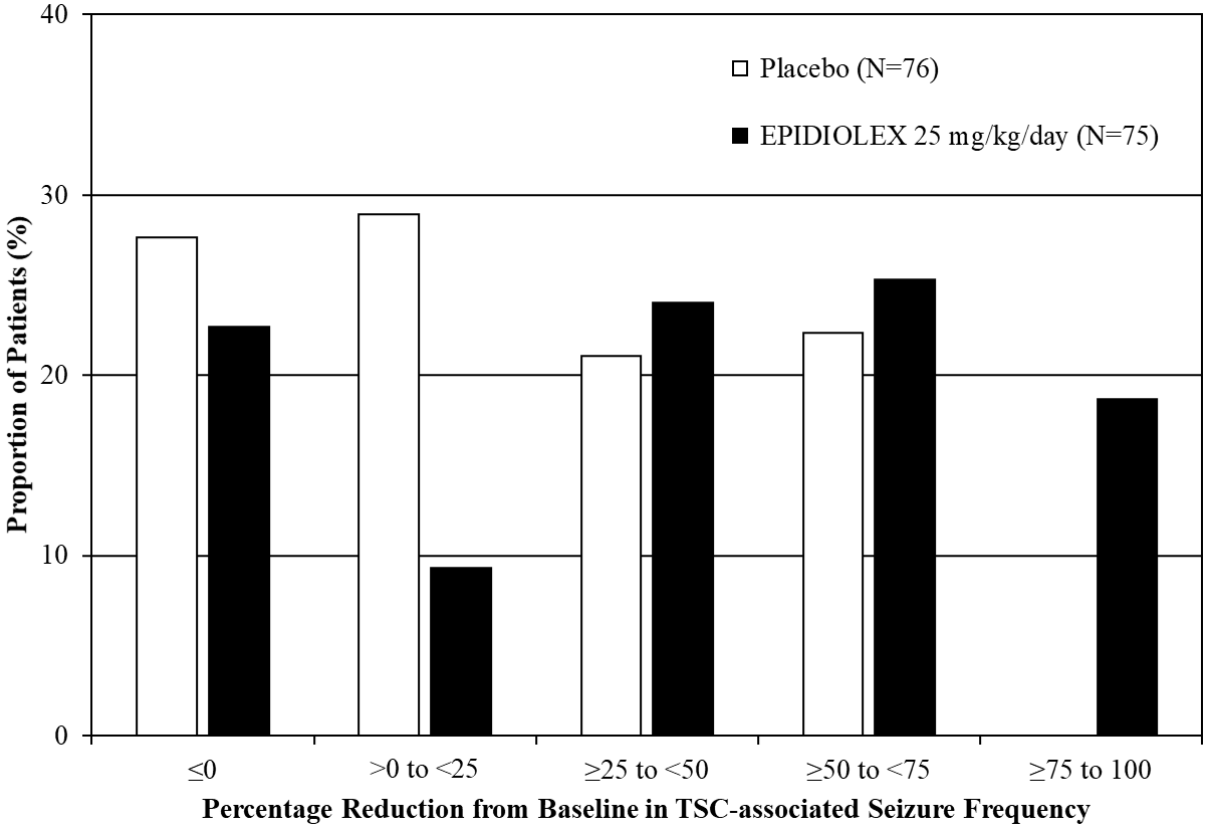
**Table 7: Change in TSC-Associated Seizure Frequency during the Treatment Period (Study 4)**

| **Total TSC-Associated Seizures (per 28 Days)** | **Placebo** | **EPIDIOLEX 25 mg/kg/day** |
|---|---|---|
| **Study 4** | **N=76** | **N=75** |
| Baseline Period Median Seizure Frequency | 54 | 56 |
| Median Percentage Change from Baseline During Treatment | −20 | −43 |
| p-value compared to placebo[a] | | <0.01 |
| Percentage Change from Baseline During Treatment in Estimated Mean Seizure Frequency[b] | −24 | −48 |
| p-value compared to placebo[b] | | <0.01 |

[a]Obtained from a Wilcoxon rank-sum test.
[b]Obtained from a log-transformed ANCOVA.

Figure 4 displays the percentage of patients by category of reduction from baseline in TSC-associated seizure frequency (per 28 days) during the treatment period in Study 4.

**Figure 4: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Tuberous Sclerosis Complex (Study 4)**




In Study 4, 4 of 71 (6%) patients treated with EPIDIOLEX 25 mg/kg/day reported no TSC-associated seizures during the maintenance period, compared to 0 patients in the placebo group.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

EPIDIOLEX is a strawberry-flavored, clear, colorless to yellow solution supplied in an amber glass bottle with a child-resistant closure. EPIDIOLEX is available in bottles containing 60 mL (NDC 70127-100-06) or 100 mL of oral solution (NDC 70127-100-01). Each mL contains 100 mg of cannabidiol. EPIDIOLEX is packaged in a carton with two 1 mL calibrated oral dosing syringes, two 5 mL calibrated oral dosing syringes, and bottle adapters (NDC 70127-100-60 or NDC 70127-100-10).

### 16.2 Storage and Handling

Store EPIDIOLEX in an upright position at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Do not freeze. Keep the cap tightly closed. Use within 12 weeks of first opening the bottle, then discard any remainder.

## 17 PATIENT COUNSELING INFORMATION

Advise the caregiver or patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration Information

Advise patients who are prescribed EPIDIOLEX to use the adapter and oral dosing syringes provided *[see Dosage and Administration (2.4) and Instructions for Use]*. Provide instructions regarding which syringe to use and how to administer the specified dose, since EPIDIOLEX is supplied with 1 mL and 5 mL oral dispensing syringes.

Instruct patients to discard any unused EPIDIOLEX oral solution after 12 weeks of first opening the bottle *[see Dosage and Administration (2.4)]*.

Hepatic Injury

Inform patients about the potential for elevations of liver enzymes. Discuss with the patient the importance of measuring hepatic laboratory values and having them evaluated by the healthcare provider before treatment with EPIDIOLEX and periodically during treatment *[see Warnings and Precautions (5.1)]*. Advise patients of the 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) and to contact a healthcare provider promptly if these signs or symptoms occur.

Somnolence and Sedation

Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that EPIDIOLEX does not affect them adversely (e.g., impair judgment, thinking or motor skills) *[see Warnings and Precautions (5.2)]*.

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and their families that antiepileptic drugs, including EPIDIOLEX, may increase the risk of suicidal thoughts and behavior and advise them to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Instruct patients, caregivers, and families to report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.3)]*.

Withdrawal of Antiepileptic Drugs (AEDs)

Advise patients not to discontinue use of EPIDIOLEX without consulting with their healthcare provider. EPIDIOLEX should normally be gradually withdrawn to reduce the potential for increased seizure frequency and status epilepticus *[see Dosage and Administration (2.5) and Warnings and Precautions (5.5)]*.

Pregnancy Surveillance Program and Pregnancy Exposure Registry

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during EPIDIOLEX therapy. Encourage women who are taking EPIDIOLEX to enroll in both the EPIDIOLEX Pregnancy Surveillance Program and the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. The surveillance program and exposure registry are collecting information about the safety of EPIDIOLEX and other antiepileptic drugs during pregnancy *[see Use in Specific Populations (8.1)]*.

Drug Testing

Advise patients of the potential for positive cannabis drug screens.

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Palo Alto, CA 94306

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**MEDICATION GUIDE**
**EPIDIOLEX® (EH-peh-DYE-oh-lex)**
**(cannabidiol)**
**oral solution**

Read this Medication Guide before you start taking EPIDIOLEX and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

**What is the most important information I should know about EPIDIOLEX?**
**EPIDIOLEX can cause serious side effects, including:**

1. EPIDIOLEX may cause liver problems. Your healthcare provider may order blood tests to check your liver before you start taking EPIDIOLEX and during treatment. In some cases, EPIDIOLEX treatment may need to be stopped. Call your healthcare provider right away if you develop any of these signs and symptoms of liver problems during treatment with EPIDIOLEX:
   - loss of appetite, nausea, vomiting
   - fever, feeling unwell, unusual tiredness
   - yellowing of the skin or the whites of the eyes (jaundice)
   - itching
   - unusual darkening of the urine
   - right upper stomach area pain or discomfort
2. EPIDIOLEX may cause you to feel sleepy, which may get better over time. Using certain medicines with EPIDIOLEX such as clobazam or alcohol may increase sleepiness. **Do not** drive, operate heavy machinery, or do other dangerous activities until you know how EPIDIOLEX affects you.
3. Like other antiepileptic drugs, EPIDIOLEX may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.
   **Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:**
   - thoughts about suicide or dying
   - attempt to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood

   **How can I watch for early symptoms of suicidal thoughts and actions?**
   - Pay attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings.
   - Keep all follow-up visits with your healthcare provider as scheduled.
4. Do not stop taking EPIDIOLEX without first talking to your healthcare provider. Stopping a seizure medicine such as EPIDIOLEX suddenly can cause you to have seizures more often or seizures that do not stop (status epilepticus).

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

**What is EPIDIOLEX?**

- EPIDIOLEX is a prescription medicine that is used to treat seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in people 1 year of age and older.
- It is not known if EPIDIOLEX is safe and effective in children under 1 year of age.

**Who should not take EPIDIOLEX?**

Do not take EPIDIOLEX if you are allergic to cannabidiol or any of the ingredients in EPIDIOLEX. See the end of this Medication Guide for a complete list of ingredients in EPIDIOLEX.

**Before taking EPIDIOLEX, tell your healthcare provider about all of your medical conditions, including if you:**

- have or have had depression, mood problems or suicidal thoughts or behavior.
- have liver problems.
- have abused or been dependent on prescription medicines, street drugs or alcohol.
- are pregnant or plan to become pregnant. Tell your healthcare provider right away if you become pregnant while taking EPIDIOLEX. You and your healthcare provider will decide if you should take EPIDIOLEX while you are pregnant. If you become pregnant while taking EPIDIOLEX, talk to your healthcare provider about registering for both the EPIDIOLEX Pregnancy Surveillance Program and the North American Antiepileptic Drug (NAAED) registry. The purpose of the surveillance program and exposure registry is to collect information about the safety of EPIDIOLEX and other antiepileptic drugs during pregnancy.
  - You can enroll in the EPIDIOLEX Pregnancy Surveillance Program by calling the toll free number 1-855-272-7158 or visiting https://www.epidiolexpregnancystudy.com.
  - You can enroll in the North American Antiepileptic Drug Pregnancy Registry by calling the toll free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org.

- are breastfeeding or plan to breastfeed. It is not known if EPIDIOLEX passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking EPIDIOLEX.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, herbal supplements, and any cannabis-based products.

EPIDIOLEX may affect the way other medicines work, and other medicines may affect how EPIDIOLEX works. Do not start or stop taking other medicines without talking to your healthcare provider. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

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

**How should I take EPIDIOLEX?**

- Read the **Instructions for Use** at the end of this Medication Guide for information on the right way to use EPIDIOLEX.
- Take EPIDIOLEX exactly as your healthcare provider tells you.
- Your healthcare provider will tell you how much EPIDIOLEX to take and when to take it.
- Measure each dose of EPIDIOLEX using the bottle adapter and the appropriate dosing syringes that come with EPIDIOLEX. If your dose of EPIDIOLEX is 1 mL or less, use the 1 mL syringes to take your medicine.
- Use a dry syringe each time you take EPIDIOLEX. If water is inside the syringe, it could cause the oil-based medicine to look cloudy.

**What should I avoid while taking EPIDIOLEX?**

- **Do not** drive, operate heavy machinery, or do other dangerous activities until you know how EPIDIOLEX affects you. EPIDIOLEX may cause you to feel sleepy.

**What are the possible side effects of EPIDIOLEX?**

**EPIDIOLEX can cause serious side effects, including:**

- See "**What is the most important information I should know about EPIDIOLEX?**"

**The most common side effects of EPIDIOLEX include:**

- sleepiness
- decreased appetite
- diarrhea
- increase in liver enzymes
- feeling very tired and weak
- rash
- sleep problems
- fever
- vomiting
- infections

These are not all of the possible side effects of EPIDIOLEX. For more information ask your healthcare provider or pharmacist.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also contact Jazz Pharmaceuticals at 1-800-520-5568.

**How should I store EPIDIOLEX?**

- Store EPIDIOLEX at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Always store EPIDIOLEX in an upright position.
- **Do not** freeze.
- Keep the child-resistant cap tightly closed.
- Use EPIDIOLEX within 12 weeks of first opening the bottle. Throw away (dispose of) any unused medicine after 12 weeks.

**Keep EPIDIOLEX and all medicines out of the reach of children.**

**General Information about the safe and effective use of EPIDIOLEX.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use EPIDIOLEX for a condition for which it was not prescribed. Do not give EPIDIOLEX to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about EPIDIOLEX that is written for health professionals.

**What are the ingredients in EPIDIOLEX?**

**Active ingredient:** cannabidiol

**Inactive ingredients:** dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose

EPIDIOLEX does not contain gluten (wheat, barley or rye).

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**INSTRUCTIONS FOR USE**
**EPIDIOLEX® (EH-peh-DYE-oh-lex)**
**(cannabidiol)**
**oral solution**
**100 mg/mL**

Be sure that you read, understand and follow these instructions carefully to ensure proper dosing of the oral solution.

**Important:**

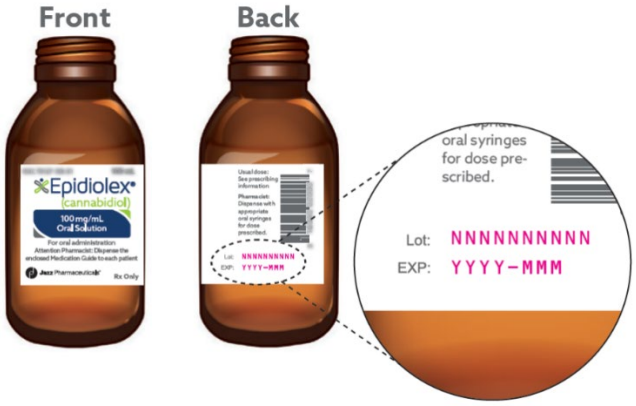
- Follow your healthcare provider's instructions for the dose of EPIDIOLEX to take or give.
- Ask your healthcare provider or pharmacist if you are not sure how to prepare, take, or give the prescribed dose of EPIDIOLEX.
- Always use the oral syringe provided with EPIDIOLEX to make sure you measure the 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 throw away (dispose of) any EPIDIOLEX that has not been used.

**Each package contains:**

Child-resistant cap

2 Bottle adapters

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



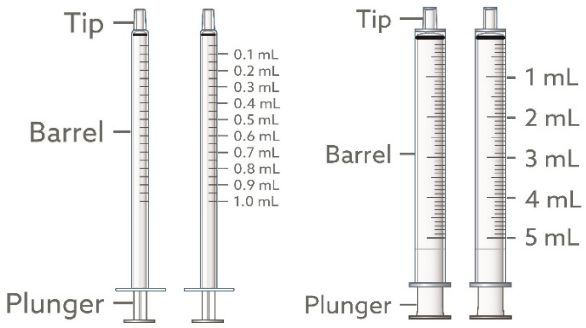

Please note expiration date.

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

**If your dose of EPIDIOLEX is 1 mL or less**, use the 1 mL syringes to take your medicine.

For each syringe size:

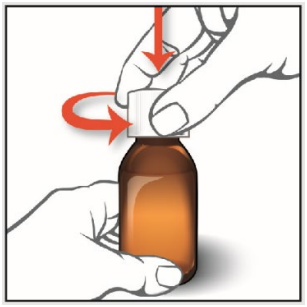
- 1 syringe to take or give the dose of EPIDIOLEX
- 1 extra syringe (included as a spare if needed)




**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 bottle adapter firmly into the bottle. **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.**

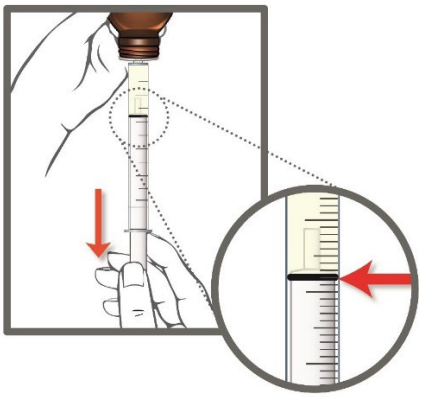
3. Use this table to measure the total dose of EPIDIOLEX to be given.

| **Dose** | **How to measure** |
|---|---|
| 1 mL or less | Use the 1 mL oral syringe **1 time** |
| More than 1 mL and less than 5 mL | Use the 5 mL oral syringe **1 time** |
| More than 5 mL | 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. See **Step 3** for how to measure the total dose of EPIDIOLEX.

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

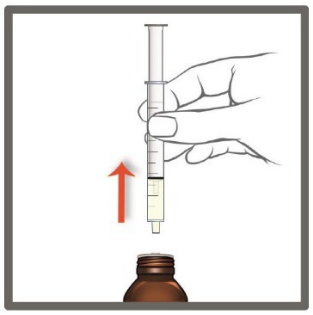


   **What to do if you see air bubbles:**

   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.

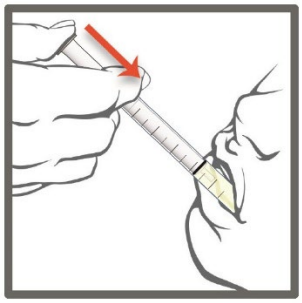
6. When you have measured the correct dose of EPIDIOLEX, leave the oral syringe in the bottle adapter and turn the bottle right side up.

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



**Give EPIDIOLEX**

8. 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.

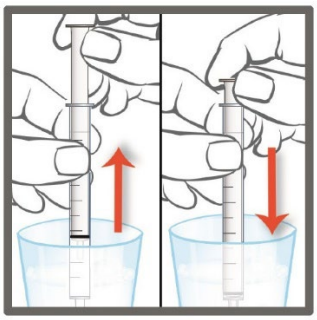
For example:
If your dose of EPIDIOLEX is 8 mL, withdraw 5 mL of medicine into the syringe and give the medicine. Insert the tip of the oral syringe back into the bottle adapter and withdraw 3 mL of medicine. Give the medicine to receive a total dose of 8 mL.

**Clean Up**

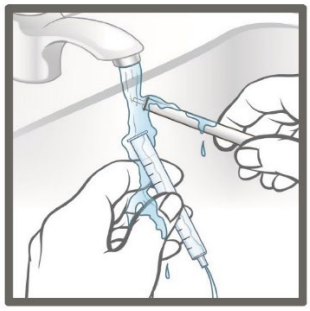
9. Screw the child-resistant cap back on the bottle tightly by turning the cap to the right (clockwise).

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

**10.** 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.

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

**How should I store EPIDIOLEX?**

- Store EPIDIOLEX at room temperature between 68°F to 77°F (20°C to 25°C).
- Always store EPIDIOLEX in an upright position.
- **Do not** freeze.
- 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 EPIDIOLEX and all medicines out of the reach of children.**

**Helpline Details**

For additional assistance, call the toll-free helpline at 1-833-426-4243.

Hours:
Monday-Friday 08:00am – 08:00pm EST

**Frequently Asked Questions**

**Q: What if there are air bubbles in the oral syringe?**
A: Push the liquid back into the bottle and repeat **Step 5** until the air bubbles are gone.

**Q: What should I do if the liquid in the bottle has turned cloudy?**
A: The liquid in the bottle may turn cloudy if water gets in the bottle. This does not change the safety or how well the medicine works. Continue to use the cloudy liquid as prescribed by your healthcare provider.
Always make sure the oral syringes are completely dry before each use.

**Q: What should I do if the oral syringe is not completely dry before use?**
A: If the oral syringe is not completely dry, use the spare syringe provided in the pack.

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Palo Alto, CA 94306

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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