Clinical review:

Concomitant use of EPIDIOLEX® (cannabidiol) and clobazam in the treatment of Lennox-Gastaut syndrome (LGS)

LGS is a severe epileptic and developmental encephalopathy associated with a high rate of morbidity and mortality. Patients experience frequent treatment-refractory seizures.[1,2]

Patients living with LGS have often tried a variety of pharmacological and non-pharmacological therapies, often in combination.[1,2]

EPIDIOLEX and clobazam are both indicated for the treatment of seizures associated with LGS:

EPIDIOLEX

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

Clobazam

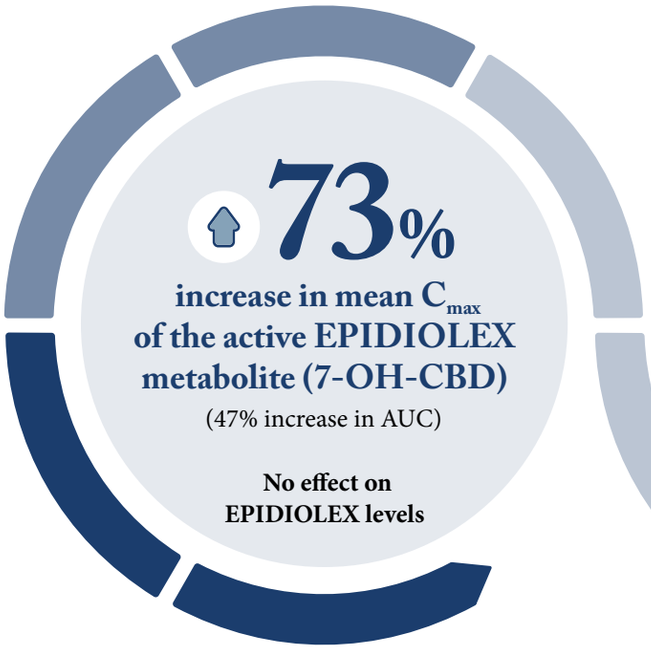
Clobazam is indicated for adjunctive treatment of seizures associated with LGS in patients 2 years of age or older.[3]

This clinical review presents data on concomitant use of EPIDIOLEX and clobazam to help inform clinical decisions

EPIDIOLEX and clobazam have a bidirectional pharmacokinetic relationship

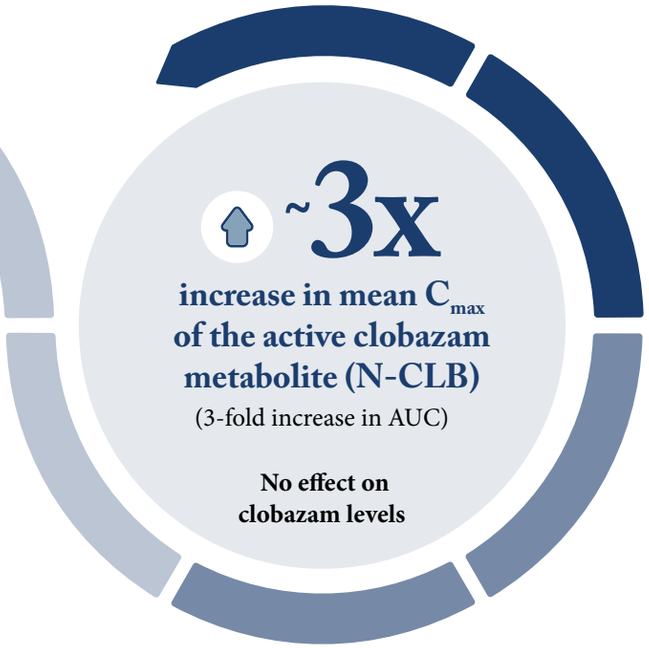
Each compound selectively increases exposure to the major active metabolite of the other without affecting parent drug levels

Clobazam effect on EPIDIOLEX



In a preclinical seizure model, the active metabolite 7-OH-CBD was 5-fold more potent than CBD[4]

EPIDIOLEX effect on clobazam



Based on preclinical studies, the active metabolite N-CLB is estimated to be from 1/5 to equal the potency of clobazam[3]

The addition of EPIDIOLEX with clobazam may increase the risk of clobazam-related adverse reactions. Consider a reduction in dosage of clobazam if adverse reactions known to occur with clobazam are experienced when coadministered with EPIDIOLEX.

Important Safety Information

Warnings & Precautions

Hepatic Injury:

EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk. Obtain transaminase and bilirubin levels prior to starting treatment, at 1, 3, and 6 months after initiation of treatment, and periodically thereafter, or as clinically indicated. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX, reduction of EPIDIOLEX and/or concomitant valproate, or without dose reduction. For patients with elevated transaminase levels, consider dose reduction or discontinuation of EPIDIOLEX or concomitant medications known to affect the liver (e.g., valproate or clobazam). Dose adjustment and slower dose titration is recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury. There have been postmarketing reports of cholestatic or mixed patterns of liver injury. Elevated ammonia levels were reported in some patients with transaminase elevations; most taking concomitant valproate, clobazam, or both. Consider discontinuation or dose adjustment of valproate or clobazam if ammonia is elevated.

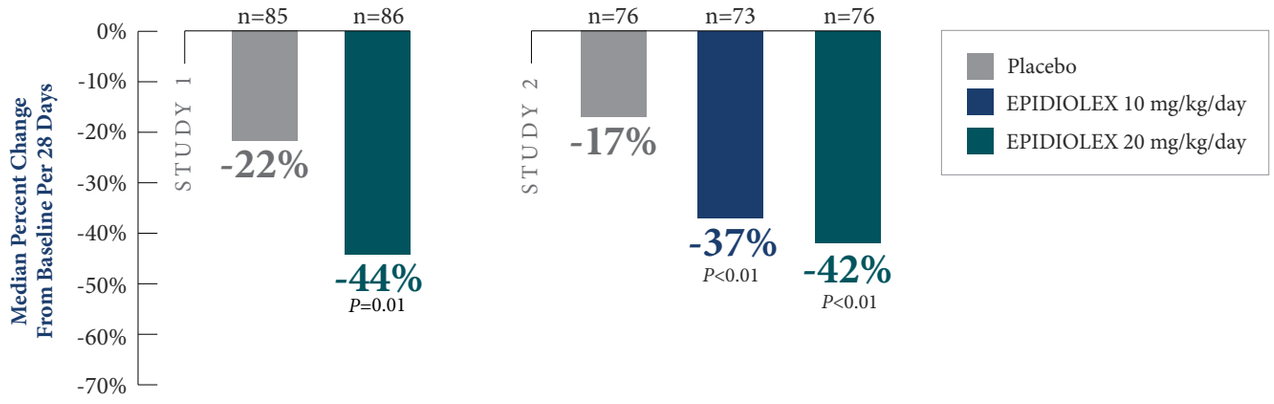
AUC=area under the curve; C_{max}=maximum serum concentration; N-CLB=N-desmethylclobazam; 7-OH-CBD=7-hydroxycannabidiol.

Please see Important Safety Information throughout and on page 11 and the full Prescribing Information.

Epidiolex® (cannabidiol)

EPIDIOLEX significantly reduced drop seizure frequency in highly refractory patients with LGS

Reduction in monthly frequency of drop seizures*

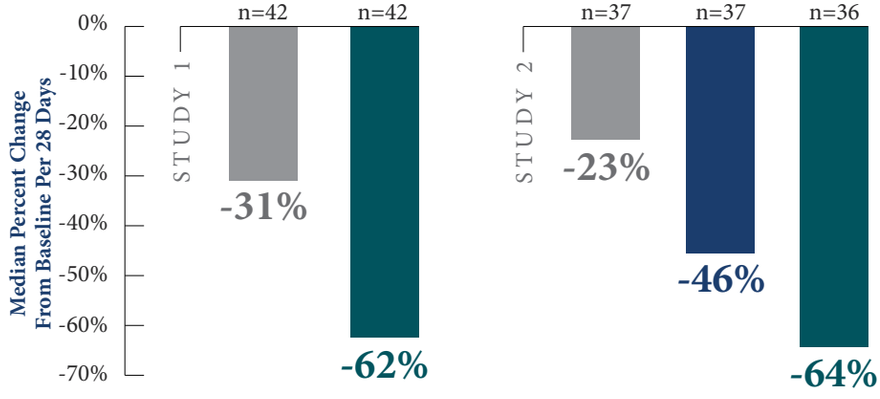


*Results from the 14-week treatment period. Drop seizures were defined as atonic, tonic, or tonic-clonic seizures that led to or could have led to a fall or injury.[5,6]

In the EPIDIOLEX clinical studies for LGS, 49% of patients were taking concomitant clobazam

A prespecified exploratory analysis evaluated the effect of EPIDIOLEX on drop seizure reduction in the subgroup of patients receiving clobazam[7]

Among patients taking clobazam, those also taking EPIDIOLEX experienced a greater reduction in drop seizures than with placebo[7]



49% of patients in LGS clinical trials were taking concomitant clobazam. Subgroup analysis is exploratory and descriptive in nature.

Patients taking clobazam and:
- Placebo
- EPIDIOLEX 10 mg/kg/day
- EPIDIOLEX 20 mg/kg/day

Important Safety Information (cont'd)

Warnings & Precautions (cont'd)

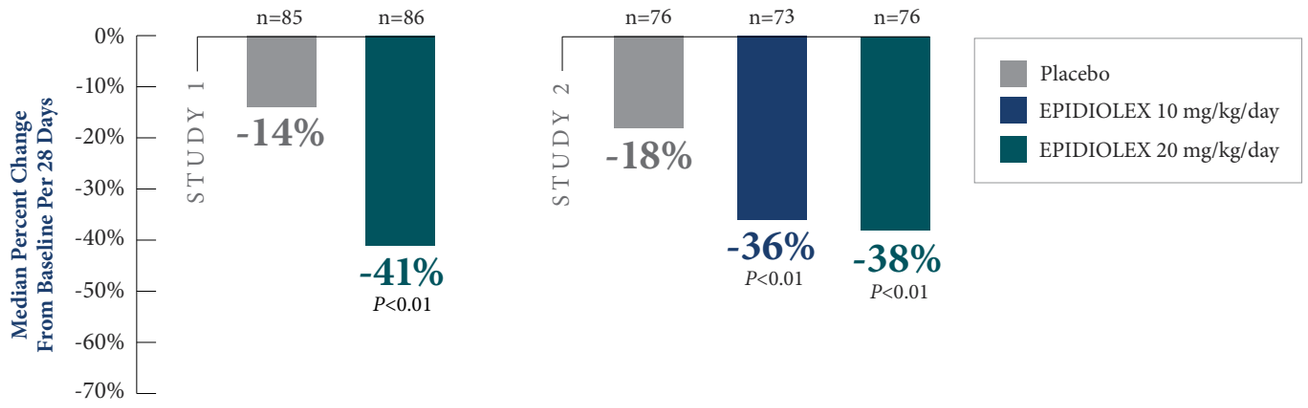
Somnolence and Sedation:
EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more commonly in patients using clobazam and may be potentiated by other CNS depressants.

Please see Important Safety Information throughout and on page 11 and the full Prescribing Information.

Epidiolex® (cannabidiol)

EPIDIOLEX significantly reduced total seizures in patients with LGS

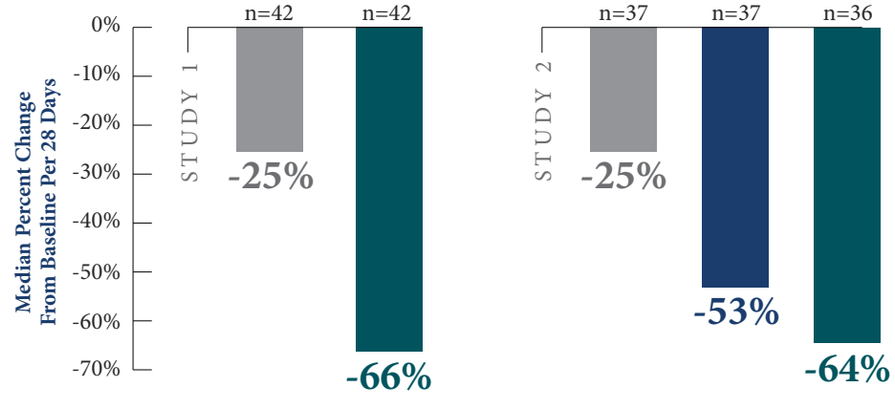
Reduction in monthly frequency of total seizures*



*Results from the 14-week treatment period. Total seizures included drop and non-drop seizures.[5,6]

A post-hoc exploratory analysis evaluated the effect of EPIDIOLEX on total seizure reduction in the subgroup of patients receiving clobazam[7]

Among patients taking clobazam, those also taking EPIDIOLEX experienced a greater reduction in total seizures than with placebo[7]



49% of patients in LGS clinical trials were taking concomitant clobazam. Subgroup analysis is exploratory and descriptive in nature.

Patients taking clobazam and:
- Placebo
- EPIDIOLEX 10 mg/kg/day
- EPIDIOLEX 20 mg/kg/day

For patients with LGS and Dravet syndrome, the recommended daily dosage of EPIDIOLEX is **10 mg/kg/day** (5 mg/kg twice daily), with a maximum maintenance dosage of **20 mg/kg/day** (10 mg/kg twice daily)*

*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. Patients with moderate to severe hepatic impairment require a dose adjustment.

Important Safety Information (cont'd)

Warnings & Precautions (cont'd)

Suicidal Behavior and Ideation:

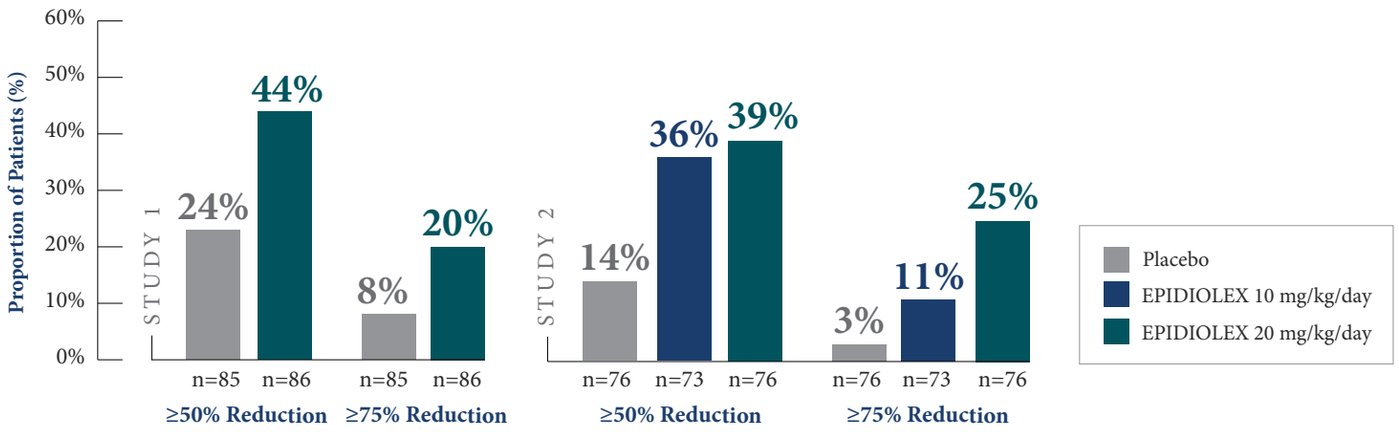
Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior. Inform patients, caregivers, and families of the risk and advise them to monitor and report any signs of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior. If these symptoms occur, consider if they are related to the AED or the underlying illness.

Please see Important Safety Information throughout and on page 11 and the full Prescribing Information.

Epidiolex® (cannabidiol)

EPIDIOLEX cut seizure frequency by ≥50% and ≥75% in more patients than placebo in the LGS trials[7]

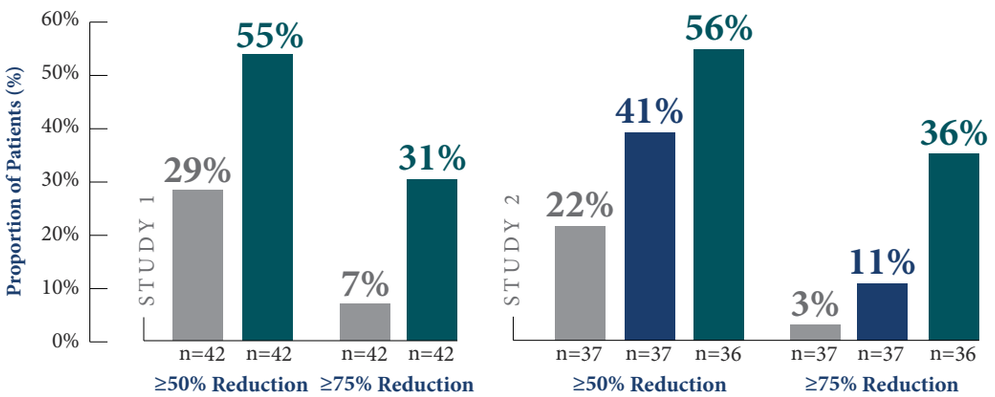
Responder rates (≥50% and ≥75% reductions in drop seizures from baseline)[7*]



*Results from the 14-week treatment period. ≥50% responder rate, defined as the proportion of patients with ≥50% reduction in primary seizure type frequency during the treatment period. ≥75% responder rate, defined as the proportion of patients with ≥75% reduction in primary seizure type frequency during the treatment period.

A prespecified exploratory analysis evaluated the effect of EPIDIOLEX on seizure frequency in the subgroup of patients receiving clobazam[7]

Among patients taking clobazam, more experienced ≥50% and ≥75% reductions in seizure frequency with EPIDIOLEX than with placebo[7]



49% of patients in LGS clinical trials were taking concomitant clobazam. Subgroup analysis is exploratory and descriptive in nature.

Patients taking clobazam and:
- Placebo
- EPIDIOLEX 10 mg/kg/day
- EPIDIOLEX 20 mg/kg/day

Important Safety Information (cont'd)

Warnings & Precautions (cont'd)

Withdrawal of Antiepileptic Drugs:
As with most AEDs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

Please see Important Safety Information throughout and on page 11 and the full Prescribing Information.

Epidiolex® (cannabidiol)

The safety profile of EPIDIOLEX was evaluated in an expansive clinical trial program

Most common adverse events (≥10% and greater than placebo) observed during the 14-Week treatment period of Phase 3 controlled trials for LGS and Dravet syndrome (%)

	Placebo (n=227)	EPIDIOLEX 10 mg/kg/day (n=75)	EPIDIOLEX 20 mg/kg/day (n=238)
Hepatic Disorders			
Transaminases elevated	3	8	16
Gastrointestinal Disorders			
Decreased appetite	5	16	22
Diarrhea	9	9	20
Nervous System Disorders			
Somnolence	8	23	25
Fatigue, malaise, asthenia	4	11	12
Insomnia, sleep disorder, poor-quality sleep	4	11	5
Infections			
Infection, all	31	41	40
Other			
Rash	3	7	13

In LGS and Dravet syndrome, EPIDIOLEX was found to have a consistent safety profile in children and adults

Hematologic abnormalities, decreased weight, and increased creatinine levels were also observed.

In the LGS and Dravet syndrome studies, the rate of discontinuation for 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 causes of discontinuation were transaminase elevations, somnolence, sedation, and lethargy.

Pneumonia was observed more frequently with concomitant use of EPIDIOLEX and clobazam.

Important Safety Information (cont'd)

Adverse Reactions:

The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include transaminase elevations; somnolence; decreased appetite; diarrhea; pyrexia; vomiting; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder and poor-quality sleep; and infections. Hematologic abnormalities were also observed.

Please see Important Safety Information throughout and on page 11 and the full Prescribing Information.

Epidiolex® (cannabidiol)

Important considerations for patients taking EPIDIOLEX and clobazam

Warnings & precautions: Somnolence and sedation

Combined incidence of somnolence and sedation (including lethargy)

LGS & Dravet syndrome clinical trials		
OVERALL	Placebo overall	11%
	EPIDIOLEX overall	32%
BY DOSE	EPIDIOLEX 10 mg/kg/day	27%
	EPIDIOLEX 20 mg/kg/day	34%
USE OF CLOBAZAM	EPIDIOLEX without clobazam	16%
	EPIDIOLEX with concomitant clobazam	46%

- 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
- Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX

In clinical trials, clobazam was among the most commonly used concomitant ASMs

Clobazam

EPIDIOLEX produces a 3-fold increase in plasma concentrations of the active metabolite of clobazam, with no effect on clobazam levels. This may increase the risk of adverse reactions, including somnolence/sedation, pneumonia, and elevation of liver enzymes and/or ammonia.

Consider a reduction of dosage of clobazam if known clobazam adverse reactions occur.

Rapid withdrawal of most ASMs can lead to increased seizure frequency and status epilepticus.

22% of patients in the LGS studies taking concomitant clobazam with either dose of EPIDIOLEX reported a dose reduction of clobazam during the trial[8]

Ongoing monitoring during treatment is recommended

Hepatic injury

EPIDIOLEX can cause dose-related transaminase elevations.

In controlled studies, the incidence of ALT elevations (>3x the upper limit of normal [ULN]) was 13% in patients with LGS and Dravet syndrome treated with 10 and 20 mg/kg/day of EPIDIOLEX, 12% in patients with TSC treated with 25 mg/kg/day of EPIDIOLEX, and 1% with placebo. Less than 1% of EPIDIOLEX-treated patients had ALT or AST 20x the ULN.

- Concomitant use of valproate and elevated transaminase levels at baseline increase this risk

Incidence of ALT elevations >3x ULN in patients treated with EPIDIOLEX

	EPIDIOLEX + clobazam and valproate	**EPIDIOLEX + clobazam** (without valproate)	**EPIDIOLEX** (without clobazam or valproate)
LGS & Dravet syndrome clinical trials	30%	4%	3%

Obtain serum transaminases (ALT and AST) and total bilirubin levels

Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes at baseline

Monitor within 1 month following changes in EPIDIOLEX dosage and addition of or changes in medications that are known to impact the liver.

Consider discontinuation or dose reduction of EPIDIOLEX or concomitant medications known to affect the liver (eg, valproate or clobazam) if liver enzyme elevations occur (transaminase levels >3x the ULN and bilirubin levels >2x the ULN, or sustained transaminase elevations >5x the ULN).

See important dosing considerations for patients with hepatic impairment on page 10.

Important Safety Information (cont'd)

Pregnancy:

EPIDIOLEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the EPIDIOLEX Pregnancy Surveillance Program and the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Please see Important Safety Information throughout and on page 11 and the full Prescribing Information.

Epidiolex® (cannabidiol)

Additional considerations for patients taking EPIDIOLEX and other therapies

Drug interactions

- Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations
- EPIDIOLEX may affect exposure to CYP2C19 substrates (eg, clobazam, diazepam, stiripentol), orally administered P-gp substrates, or other substrates. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary
- Increases in exposure of sensitive CYP1A2 substrates (eg, caffeine, theophylline, or tizanidine) may be observed when coadministered with EPIDIOLEX

Effect on EPIDIOLEX	Dose adjustment based on tolerability
Strong inducer of CYP3A4 and CYP2C19	Consider up to a 2-fold **dose increase** of EPIDIOLEX

EPIDIOLEX effect on other substrates	
Substrates of UGT1A9, UGT2B7, CYP1A2, CYP2C8, CYP2C9, and CYP2C19	Consider **dose reduction** of the substrate
Substrates of CYP2B6	Consider **adjusting dosage** of the substrate
Orally administered substrates of P-gp	Consider **dose reduction** of the substrate and monitor therapeutic levels; recommend lower starting dose of everolimus

Important Safety Information (cont'd)

Drug Interactions:

Strong inducers of CYP3A4 and CYP2C19 may affect EPIDIOLEX exposure. EPIDIOLEX may affect exposure to CYP2C19 substrates (e.g., clobazam, diazepam, stiripentol), orally administered P-gp substrates, or other substrates (see full Prescribing Information). Consider dose reduction of orally administered everolimus, with appropriate therapeutic drug monitoring, when everolimus is combined with EPIDIOLEX. A lower starting dose of everolimus is recommended when added to EPIDIOLEX therapy. Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. Pneumonia was observed more frequently with concomitant use of EPIDIOLEX and clobazam. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary.

Please see Important Safety Information throughout and on page 11 and the full Prescribing Information.

Epidiolex® (cannabidiol)

EPIDIOLEX offers flexible dosing for tolerability and response optimization

	Recommended starting dosage	Dosage increase*	Recommended maintenance dosage
LGS	Week 1: **5 mg/kg/day** (2.5 mg/kg twice daily)	Weekly increments, as tolerated, of **5 mg/kg/day** (2.5 mg/kg twice daily)	**10 to 20 mg/kg/day**† (5 to 10 mg/kg twice daily)

EPIDIOLEX can cause dose-related elevations of liver transaminases. Because of the risk of hepatic injury, obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment with EPIDIOLEX and periodically thereafter or as clinically indicated.

*For patients in whom a more rapid titration is warranted, the dosage may be increased no more frequently than every other day.

†For patients with LGS or Dravet syndrome, 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. Increase dose from 10 mg/kg/day if tolerated and required.

EPIDIOLEX dose adjustments in patients with hepatic impairment

- Dose adjustment and slower dose titration are recommended in patients with moderate or severe hepatic impairment
- Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury
- Dose adjustments are not required in patients with mild hepatic impairment

Dosing in patients with hepatic impairment

	Starting dosage	**LGS** Maintenance dosage range
Moderate hepatic impairment (1/2 recommended standard dosing)	**2.5 mg/kg/day** (1.25 mg/kg twice daily)	**5 to 10 mg/kg/day** (2.5 to 5 mg/kg twice daily)
Severe hepatic impairment (1/5 recommended standard dosing)	**1 mg/kg/day** (0.5 mg/kg twice daily)	**2 to 4 mg/kg/day** (1 to 2 mg/kg twice daily)

Please see Important Safety Information throughout and on page 11 and the full Prescribing Information.

Epidiolex® (cannabidiol)

Important Safety Information & Indications

Contraindication: Hypersensitivity

EPIDIOLEX (cannabidiol) oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or any ingredients in the product.

Warnings & Precautions

Hepatic Injury:
EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk. Obtain transaminase and bilirubin levels prior to starting treatment, at 1, 3, and 6 months after initiation of treatment, and periodically thereafter, or as clinically indicated. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX, reduction of EPIDIOLEX and/or concomitant valproate, or without dose reduction. For patients with elevated transaminase levels, consider dose reduction or discontinuation of EPIDIOLEX or concomitant medications known to affect the liver (e.g., valproate or clobazam). Dose adjustment and slower dose titration is recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury. There have been postmarketing reports of cholestatic or mixed patterns of liver injury. Elevated ammonia levels were reported in some patients with transaminase elevations; most taking concomitant valproate, clobazam, or both. Consider discontinuation or dose adjustment of valproate or clobazam if ammonia is elevated.

Somnolence and Sedation:
EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more commonly in patients using clobazam and may be potentiated by other CNS depressants.

Suicidal Behavior and Ideation:
Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior. Inform patients, caregivers, and families of the risk and advise them to monitor and report any signs of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior. If these symptoms occur, consider if they are related to the AED or the underlying illness.

Withdrawal of Antiepileptic Drugs:
As with most AEDs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

Adverse Reactions:

The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include transaminase elevations; somnolence; decreased appetite; diarrhea; pyrexia; vomiting; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder and poor-quality sleep; and infections. Hematologic abnormalities were also observed.

Pregnancy:

EPIDIOLEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the EPIDIOLEX Pregnancy Surveillance Program and the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

Drug Interactions:

Strong inducers of CYP3A4 and CYP2C19 may affect EPIDIOLEX exposure. EPIDIOLEX may affect exposure to CYP2C19 substrates (e.g., clobazam, diazepam, stiripentol), orally administered P-gp substrates, or other substrates (see full Prescribing Information). Consider dose reduction of orally administered everolimus, with appropriate therapeutic drug monitoring, when everolimus is combined with EPIDIOLEX. A lower starting dose of everolimus is recommended when added to EPIDIOLEX therapy. Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. Pneumonia was observed more frequently with concomitant use of EPIDIOLEX and clobazam. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary.

Indications:

EPIDIOLEX (cannabidiol) oral solution 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.

Please read the EPIDIOLEX full Prescribing Information for additional important information.

Epidiolex® (cannabidiol)

Clinical review:

Concomitant use of EPIDIOLEX® (cannabidiol) and clobazam in the treatment of Lennox-Gastaut syndrome (LGS)

There is a bidirectional pharmacokinetic interaction between EPIDIOLEX and clobazam in which each compound selectively increases exposure to the major active metabolite of the other without affecting parent drug levels.

EPIDIOLEX significantly reduced seizure frequency in highly refractory patients with LGS.

- 49% of patients studied were on concomitant clobazam
- In a prespecified exploratory analysis that evaluated the effect of EPIDIOLEX in the subgroup of patients with LGS taking clobazam, those also taking EPIDIOLEX experienced a greater reduction in seizure frequency than with placebo[7]

Incidence of ALT elevations >3x ULN in patients treated with EPIDIOLEX in combination with clobazam (without valproate) was 4% and 3% without clobazam or valproate.

EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more commonly in patients using clobazam and may be potentiated by other CNS depressants.

- 22% of patients in the LGS studies taking concomitant clobazam with either dose of EPIDIOLEX reported a dose reduction of clobazam during the trial[8]

See how your patients can benefit from combination therapy at EPIDIOLEXhcp.com

Adverse reactions:

The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include:

- Transaminase elevations
- Somnolence
- Decreased appetite
- Diarrhea
- Pyrexia
- Vomiting
- Fatigue, malaise, and asthenia
- Rash
- Insomnia, sleep disorder, and poor-quality sleep
- Infections

Hematologic abnormalities, decreased weight, and increased creatinine levels were also observed.

References: 1. Cross JH, Auvin S, Falip M, Striano P, Arzimanoglou A. *Front Neurol*. 2017;8:505. **2.** Piña-Garza JE, Boyce D, Tworek DM, et al. *Epilepsy Behav*. 2019;90:148-153. **3.** Onfi [package insert]. Deerfield, IL: Lundbeck; 2024. **4.** Rana RR, Gray RA, Whalley BJ. Presented at: The American Epilepsy Society Annual Meeting; December 6-10, 2019; Baltimore, MD. **5.** Thiele EA, Marsh ED, French JA, et al. *Lancet.* 2018;391(10125):1085-1096. **6.** Devinsky O, Patel AD, Cross JH, et al. *N Engl J Med.* 2018;378(20):1888-1897. **7.** Gunning B, Mazurkiewicz-Bełdzińska M, Chin RFM, et al. *Acta Neurol Scand.* 2021;143(2):154-163. **8.** Data on file. Jazz Pharmaceuticals, Inc.

Please see Important Safety Information throughout and on page 11 and the full Prescribing Information.

Jazz Pharmaceuticals

Epidiolex® (cannabidiol)