

# Treatment Approaches for Adults Living With LGS

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## The Challenges of Managing Adults With LGS

Lennox-Gastaut Syndrome (LGS) is a childhood-onset epilepsy syndrome that can be challenging to diagnose in adults. Its presenting features in childhood are multiple seizure types that often include seizure-induced falls, developmental slowing or regression, and an electroencephalogram (EEG) that has a characteristic abnormality termed “slow spike and wave.”<sup>1</sup>

However, as the patient grows from childhood through adolescence and into adulthood, there are changes to the seizure types and the EEG abnormality that can overlap with the features of other epilepsy syndromes. This produces a distinct challenge while caring for adults living with LGS.<sup>1,2</sup> As another challenge, many adults living with LGS have tried multiple antiseizure medications due to years of inadequate seizure control, yet details of this treatment history are often not available or lost in the continuation of care. Additionally, adults living with LGS typically experience cognitive impairment across a broad range of intellectual function, and sometimes have behavioral issues such as hyperactivity and aggression.<sup>3</sup>

“An accurate and specific diagnosis is the first step toward better outcomes.”

— Dr John Stern

Compounding these challenges, individuals living with LGS often reach adulthood without a specific diagnosis, which may lead to suboptimal treatment. “I think the most important, also the first, step in managing adults is recognizing that it’s LGS,” says Dr John Stern, professor in the Department of Neurology and director of the Epilepsy Clinical Program at the Geffen School of Medicine at the University of California, Los Angeles. “Often patients present to the adult epileptologist or general neurologist with a history of seizures and developmental disability, and the history doesn’t include the term LGS. Recognizing LGS is then a matter of it coming to mind and knowing that a specific diagnosis within epilepsy can be useful.” A diagnosis of LGS may then help patients access appropriate treatment options for their seizures.

### 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.

### IMPORTANT SAFETY INFORMATION

#### CONTRAINDICATION: HYPERSENSITIVITY

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

Please see Important Safety Information throughout and the full [Prescribing Information](#).

# EPIDIOLEX: Proven Efficacy for Adults With LGS

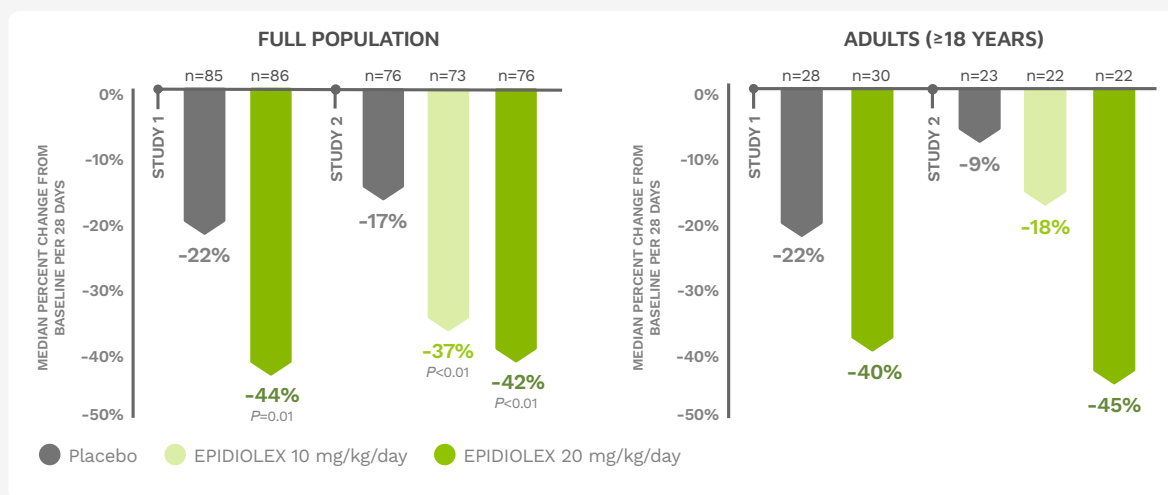
Given the realities of the condition, the main goal of treatment for many adult patients with LGS is not necessarily to achieve seizure freedom, but rather, to balance optimal seizure reduction with the side effects of treatment.<sup>2</sup>

With demonstrated seizure reduction in patients with LGS, EPIDIOLEX may be an appropriate treatment option. In 2 phase 3 clinical trials, EPIDIOLEX significantly reduced the frequency of drop and total seizures in patients ages 2 to 55 with LGS.<sup>4,6</sup>

The effect of EPIDIOLEX specifically in adult patients with LGS is demonstrated in prespecified exploratory subgroup analyses. Adult patients ( $\geq 18$  years) taking EPIDIOLEX 10 mg/kg/day or 20 mg/kg/day experienced a greater reduction in the monthly frequency of drop seizures than those taking placebo.

## Reduction in Monthly Frequency of Drop Seizures<sup>\*,1-4</sup>

### Prespecified Exploratory Subgroup Analysis: Drop Seizure Reduction in Adult Patients



Note: Adult data represent  $\sim 1/3$  of the total trial population.<sup>2,3</sup> Subgroup analysis is exploratory and descriptive in nature.<sup>4</sup>

Administration of dosages higher than 10 mg/kg/day resulted in somewhat greater reductions in seizure rates, but with an increase in adverse reactions.<sup>1</sup>

## IMPORTANT SAFETY INFORMATION (CONT'D)

### 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.

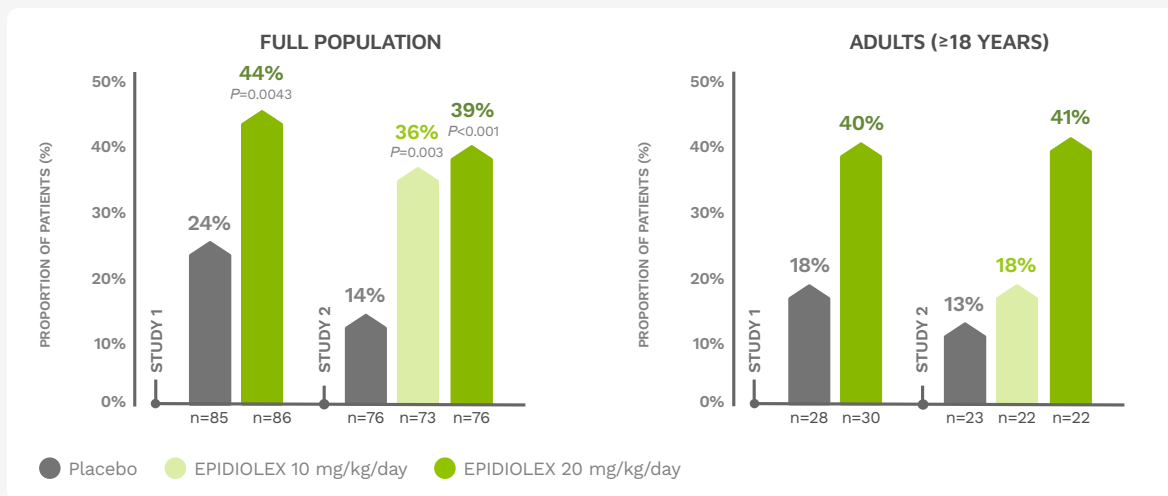
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## EPIDIOLEX: Proven Efficacy for Adults With LGS (cont'd)

Additionally, a higher proportion of adults in both dosage groups of EPIDIOLEX experienced a  $\geq 50\%$  reduction in drop seizures as compared with placebo.<sup>5</sup> In the full and adult patient population, administration of EPIDIOLEX at 20 mg/kg/day resulted in greater reduction in seizures, but with an increase in adverse reactions.

Responder Rates ( $\geq 50\%$  Reductions in Drop Seizures from Baseline)\*<sup>1-4</sup>

### Prespecified Exploratory Subgroup Analysis: $\geq 50\%$ Seizure Reduction in Adult Patients



Note: Adult data represent  $\sim 1/3$  of the total trial population.<sup>2,3</sup> Subgroup analysis is exploratory and descriptive in nature.<sup>4</sup>

\*Results from the 14-week treatment period.<sup>2,3</sup>

To start EPIDIOLEX in adults, it is important to consider the recommended maintenance dosage for tolerability and response optimization. EPIDIOLEX is started at 5 mg/kg/day and is recommended to titrate in weekly increments of 5 mg/kg/day as tolerated.

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

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

“Typically, I see that the seizure reduction is dose dependent, so getting into the higher range can provide further benefit. Stopping prematurely by not trialing EPIDIOLEX at the higher end of the maintenance dosing range means not using what you have already decided to try to its fullest potential.”

— Dr John Stern

#### 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 the full [Prescribing Information](#).

## EPIDIOLEX Offers Flexible Dosing For Adults With LGS

In considering titration schedules, Dr Stern recommends that clinicians, “titrate to a dose that has some evidence of benefit but tends to be in the low range for any tolerability issues, is less likely to cause side effects, and allows a patient to return for follow-up to discuss tolerability and any signs of benefit. Calculating the dose for an individual patient based on their weight is simple and should not be a deterrence to using EPIDIOLEX at appropriate doses.”

## Safety Considerations on the Use of EPIDIOLEX in Adults With LGS

It is also important to consider potential adverse events that may occur.

Most Common AEs (≥10% and Greater Than Placebo) in Patients With LGS		
• Somnolence	• Fatigue	• Insomnia
• Decreased Appetite	• Malaise	• Sleep Disorder
• Diarrhea	• Asthenia	• Poor-quality Sleep
• Transaminase Elevations	• Rash	• Infections

In all 3 indications, EPIDIOLEX was found to have a consistent safety profile in children and adults.

EPIDIOLEX can cause dose-related elevations of liver transaminases. Because of the risk of hepatic injury, it is important to obtain serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and total bilirubin levels in all patients prior to starting treatment with EPIDIOLEX and periodically thereafter or as clinically indicated.<sup>4</sup> Dr Stern details that, “When thinking of treatment options, you need to think about the safety and tolerability profiles. Some patients may be more sensitive to sedation or gastrointestinal side effects. Determining tolerability must be considered on an individual basis.”

Managing drug interactions is also a key consideration, as treatment regimens for adults will likely include concomitant ASMs. In the LGS clinical trials, clobazam and valproate were among the most commonly used concomitant ASMs. As EPIDIOLEX produces a 3-fold increase in plasma concentrations of the active metabolite of clobazam (with no effect of clobazam levels), the risk of clobazam-related adverse reactions may increase with concomitant use. These adverse reactions may include somnolence/sedation, pneumonia, and liver enzyme elevations.<sup>4</sup> Dosing adjustments should be made by clinicians based on individual patient response, tolerability, and physician experience.

“I have many patients using clobazam and EPIDIOLEX. When those two are used in combination, there is a greater sensitivity to the side effect of drowsiness. A reduction of the clobazam dose is typically helpful in reaching an EPIDIOLEX dose that may have a greater advantage.”

— Dr John Stern

A dose reduction of clobazam is recommended if known clobazam adverse reactions occur.

### 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.

##### 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 the full [Prescribing Information](#).

## Safety Considerations on the Use of EPIDIOLEX in Adults With LGS (cont'd)

Coadministration of EPIDIOLEX with valproate increases the incidence of liver enzyme elevation. In drug interaction studies, there was no clinically relevant effect on valproate exposure. Ongoing liver monitoring is recommended, especially in patients taking both EPIDIOLEX and valproate, clobazam or other concomitant medications known to affect the liver.<sup>4</sup>

### Incidence Of ALT Elevations >3x The ULN In Patients With LGS And Dravet Syndrome Treated With Epidiolex

	LGS & Dravet syndrome clinical trials
EPIDIOLEX + clobazam and valproate	30%
EPIDIOLEX + valproate (without clobazam)	21%
EPIDIOLEX + clobazam (without valproate)	4%
EPIDIOLEX (without clobazam and valproate)	3%

### Overall Population Of Patients With LGS, Dravet Syndrome, And TSC

Elevations resolved in 2/3 of patients following:

- Discontinuation of EPIDIOLEX, or
- Reduction of EPIDIOLEX and/or concomitant valproate

And in 1/3 of patients:

- With no change in EPIDIOLEX treatment

Elevations typically occurred within the first 2 months of treatment; however, there were some cases observed up to 18 months after initiation

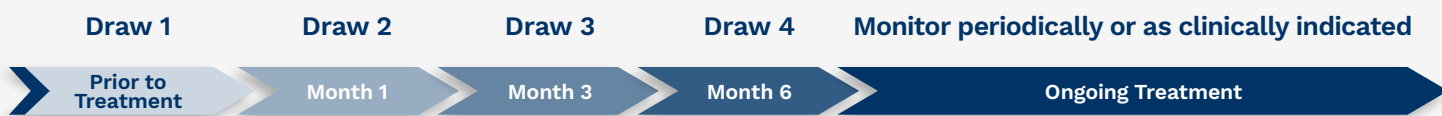
- There were cases of transaminase elevations associated with hospitalization

**Risk factors** for elevated transaminases include:

1. Increased EPIDIOLEX dose
2. Concomitant use of valproate and, to a lesser extent, clobazam
3. Baseline transaminase elevations

Less than 1% of EPIDIOLEX patients had ALT or AST >20x the ULN.

## 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).

### 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 the full [Prescribing Information](#).

## Treating Adults With LGS

Adults living with LGS have unique needs and challenges that should be at the forefront of clinical decision-making. Treatment approaches for this patient population should consider the need for seizure reduction balanced with the overall tolerability of the regimen.<sup>2</sup> With a consistent safety profile and the ability to dose for optimized treatment response and tolerability, EPIDIOLEX should be considered an appropriate ASM choice for adults with LGS.<sup>3,5</sup>

“Maximizing seizure control with the fewest side effects at a specific dose is going to vary across individuals, but we should be taking advantage of the clinical data that exist in choosing treatments for patients diagnosed with LGS. With EPIDIOLEX, I find the recommended dosing schedule to be worthwhile, and we’re fortunate that the safety profile has not greatly changed over the years with many, many more people having used it.”

— Dr John Stern

### IMPORTANT SAFETY INFORMATION (CONT'D)

#### ADVERSE REACTIONS:

The most common adverse reactions in patients receiving EPIDIOLEX ( $\geq 10\%$  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.

**Please read the EPIDIOLEX full [Prescribing Information](#) for additional important information.**

#### References:

1. Patel AD, Mazurkiewicz-Beldzińska M, Chin RF, et al. *Epilepsia*. 2021;62(9):2228-2239.
2. van Rijkevorseel K. *Neuropsychiatr Dis Treat*. 2008;4(6):1001-1019.
3. Ferlazzo E, Nikaronova M, Italiano D, et al. *Epilepsy Res*. 2010;89(2-3):271-277.
4. EPIDIOLEX [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2024.
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6. Privitera M, Bhathal H, Wong M, et al. *Epilepsia*. 2021;62(5):1130-1140.