

INTRODUCTION

The table below summarizes current labeling and literature on the treatment with antiseizure medications (ASMs) of patients whose hepatic function is impaired. The table is updated to June 2026. It is aimed at helping clinicians who provide care for persons with epilepsy in adjusting treatment for those with mild, moderate, and severe hepatic disease. The dosing recommendations refer to adults. The table is followed by a figure that summarizes the changes in exposure to ASMs in patients with impaired hepatic function.

BACKGROUND

Hepatic dysfunction primarily affects the pharmacokinetics of ASMs, which are mostly or exclusively excreted by the liver. However, it can also alter protein binding, thereby affecting “renal” drugs. The effects of hepatic dysfunction additionally depend on the fraction of the dose metabolized by the liver, protein binding of the drug, and the dependence of its pharmacokinetics on hepatic blood flow. Additionally, changes in hepatic function may differently alter the activities of individual drug-metabolizing enzymes. Unlike in renal dysfunction, no specific markers of liver function that can currently be used to guide dosage adjustments. The severity of hepatic disease is assessed using the Child-Pugh categories. Grades A, B, and C generally indicate mild, moderate, and severe impairment of hepatic function, and the table is organized accordingly. Specific conditions such as hepatitis and hepatic steatosis are described if data are available.

TARGET AUDIENCE

The American Epilepsy Society Treatments Committee provides this document for neurologists, pharmacists, nurses, and other specialists who treat persons with epilepsy and for basic scientists who are interested in ASM treatment.

IMPORTANT NOTES

- This document summarizes prescribing and literature data and is not intended to constitute treatment recommendations.
- Recommended ASMs for patients with hepatic dysfunction include levetiracetam and gabapentin. Lacosamide and oxcarbazepine may also be considered, ¹ but the lacosamide doses should be adjusted, and its administration to patients with severe hepatic failure is not recommended.² In addition, no data are available regarding the pharmacokinetics of oxcarbazepine in patients with severe hepatic failure. Lorazepam is a good choice for initial treatment of convulsive status epilepticus. Dose adjustment may be required for some ASMs that are primarily eliminated by the liver. ASMs that can cause severe hepatic damage, such as felbamate and valproic acid, should be avoided. ^{1,3}
- Patients with impaired hepatic function should be closely monitored for seizure activity and for adverse reactions of ASMs or those related to the accumulation of endogenous compounds (e.g., ammonia). For highly protein-bound ASMs, the unbound concentrations in serum provide better guidance for dose adjustment than total concentrations. Using the latter may lead to overdosage.

Antiseizure Medications and Hepatic Dysfunction Chart



Child-Pugh Grade A		Child-Pugh Grade B		Child-Pugh Grade C	
Adrenocortico-tropic hormone (ACTH)					
	Dose: Potential enhanced effect with liver cirrhosis. ⁴				
No Comments					
Brivaracetam					
	Dose: Initial dosage: 25 mg twice daily (50 mg per day). Maximum maintenance dosage: 75 mg twice daily (150 mg per day). ⁵				
Primarily metabolized by amidases, and secondarily by CYP2C19. ⁵ In patients with hepatic cirrhosis with Child-Pugh grading A, B, and C, brivaracetam exposure increased 1.50-, 1.57-, and 1.59-fold, respectively. ⁶					
Cannabidiol					
	No change Starting dose: 2.5 mg/kg twice daily (5 mg/kg/day) Maintenance dose in patients with LGS or DS: 5 to 10 mg/kg twice daily (10 to 20 mg/kg/day) Maintenance dose in patients with TSC: 12.5 mg/kg twice daily (25 mg/kg/day). ⁷	Dose: Starting dose: 1.25 mg/kg twice daily (2.5 mg/kg/day) Maintenance dose in patients with LGS or DS: 2.5 to 5 mg/kg twice daily (5 to 10 mg/kg/day) Maintenance dose in patients with TSC: 6.25 mg/kg twice daily (12.5 mg/kg/day). ⁷	Dose: Starting dose: 0.5 mg/kg twice daily (1 mg/kg/day) Maintenance dose in patients with LGS or DS: 1 to 2 mg/kg twice daily (2 to 4 mg/kg/day) Maintenance dose in patients with TSC: 2.5 mg/kg twice daily (5 mg/kg/day). ⁷		
Primarily metabolized by UGTs, also by several CYP isoforms. 7-OH-BD is an active metabolite. ⁸ In patients with hepatic impairment (Child-Pugh grading A and B), cannabidiol exposure increased 1.48- and 2.45-fold, respectively. The respective values for 7-OH-CBD were 1.10 and 2.12. ⁹					
Carbamazepine					
	Dose: (use with caution) ¹⁰ Should be avoided if possible in patients with new-onset acute hepatic dysfunction. ¹¹ Both signs of toxicity and serum concentrations of carbamazepine should be monitored. Total concentrations may not reflect the unbound carbamazepine concentrations. ¹¹				
Primarily metabolized in the liver; the effect of hepatic impairment on pharmacokinetics is not known. ¹⁰ The doses of CYP3A4-metabolized drugs, including carbamazepine, may have to be decreased in mild cirrhosis using TDM to guide dosing. ¹¹					

Child-Pugh Grade A

Child-Pugh Grade B

Child-Pugh Grade C

Cenobamate

Dose: Maximum dose 200 mg/day. Additional dosage reduction may be considered. ¹²

Dose: Maximum dose 200 mg/day. Additional dosage reduction may be considered. ¹²

Not recommended ¹²

Extensively metabolized, primarily UGTs, and by several CYP isozymes. ¹² Cenobamate plasma AUC increased 1.9-fold, 2.3-fold, and 4.2-fold in patients with mild, moderate, and severe hepatic impairment. ¹²

Clobazam

Dose: 5 mg/day initiation with titration according to weight to ½ of total recommended dose by weight. Proceed slowly with dosing escalation. If necessary, start an additional titration on day 21 to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group). ¹³

Dose: 5 mg/day initiation with titration according to weight to ½ of total recommended dose by weight. Proceed slowly with dosing escalation. If necessary, start an additional titration on day 21 to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group). ¹³

Not recommended ¹³

Extensively metabolized mostly by CYP3A4. The primary metabolite, N-desmethyclobazam, is pharmacologically active and is predominantly metabolized by CYP2C19. The C_{max} and the AUC of clobazam (calculated from reported clearance), and the C_{max} of the metabolite did not differ in patients with mild-to-severe hepatic impairment. ^{14,15} Based on studies with sensitive CYP substrates, considerable decrease in the activity of CYP2C19 in mild, moderate, and severe hepatic cirrhosis; ¹⁶⁻¹⁸ a milder decrease in CYP2C9 activity in patients with severe cirrhosis. ^{11,19} Decreased CYP2C19 activity among pediatric patients (12-21 YO) with NASH (71% decrease in omeprazole metabolic ratio) ²⁰

Clonazepam

Dose:
Caution required. ¹³
Lower initial dose and slower titration. ¹¹

Dose:
Caution required. ¹³
Lower initial dose and slower titration. ¹¹

Contraindicated in patients with clinical or biochemical evidence of significant liver disease. ²¹

There are no published studies on the pharmacokinetics of clonazepam in patients with hepatic disease. Based on studies of other CYP3A4 substrates, clonazepam doses may need to be reduced in mild to severe cirrhosis. ¹¹

Eslicarbazepine acetate

No change: Dosage adjustments not required. ²²

No change: Dosage adjustments not required. ²²

Not recommended: Use in patients with severe hepatic dysfunction is not recommended. ²²

Eslicarbazepine acetate is a pro-drug that is hydrolyzed to eslicarbazepine. Eslicarbazepine is metabolized (40 %) by UGT isozymes. ¹¹ In patients with moderate hepatic cirrhosis, first-pass metabolism of the pro-drug was slightly decreased and the pharmacokinetics of eslicarbazepine were not altered. ²³

Child-Pugh Grade A

Child-Pugh Grade B

Child-Pugh Grade C

Ethosuximide

Dose: Label recommends utilizing extreme caution when utilizing in patients with known liver disease due to ethosuximide's potential impact on the liver²⁴ A dose reduction may be required.²⁵

Hepatic impairment pharmacokinetics not evaluated, but since ethosuximide is metabolized by CYP3A4, hepatic impairment may lead to decreased clearance and increased concentrations.¹¹

Everolimus

Dose: TSC-associated renal angiomyolipoma: 7.5 mg orally once daily; decrease the dose to 5 mg orally once daily if a dose of 7.5 mg once daily is not tolerated.²⁶

Dose: TSC-associated renal angiomyolipoma: 5 mg orally once daily; decrease the dose to 2.5 mg orally once daily if a dose of 5 mg once daily is not tolerated.²⁶

Dose: TSC-associated focal-onset seizures: 2.5 mg/m² orally once daily; Adjust dose based on everolimus trough concentrations as recommended.²⁶ According to EMA, everolimus is only recommended if the desired benefit outweighs the risk. 2.5 mg daily must not be exceeded.²⁷

Dose adjustments should be made if a patient's hepatic status changes during treatment.²⁷ Everolimus is a sensitive CYP3A substrate.²⁸ The concentrations of another sensitive CYP3A substrate, oral midazolam, were 2.4-fold higher in patients with NASH; might be attributed to body weight.²⁹

Felbamate

Contraindicated: Do not initiate in active liver disease or history of hepatic dysfunction; baseline and periodic AST/ALT monitoring recommended.^{11,30}

High hepatotoxicity potential. Eliminated unchanged by the kidneys (50 %), by glucuronidation (20 %), and by CYP isozymes (20 %).¹¹ Pharmacokinetics in patients with hepatic impairment not evaluated.^{11,30}

Fenfluramine

Dose: 20 mg/day without stiripentol; 13 mg/day with stiripentol + clobazam.³¹

Dose: 20 mg/day without stiripentol; use not recommended with stiripentol + clobazam.³¹

Dose: 17 mg/day without stiripentol; use not recommended with stiripentol + clobazam.³¹

Combined molar exposures of fenfluramine and norfenfluramine increase in hepatic impairment (Child-Pugh A/B/C); dosage adjustment required.^{31,32}

Child-Pugh Grade A

Child-Pugh Grade B

Child-Pugh Grade C

Gabapentin

No change: No specific dosing guidelines provided. ³³

No change: If hepatorenal syndrome is present, dose reduction and increase in frequency would be required in renal impairment. ³¹

Excreted unchanged in urine, with no hepatic metabolism, and has not been associated with hepatotoxicity. ¹¹ Gabapentin pharmacokinetics have not been formally studied in patients with liver failure. ³⁴

Ganaxolone

No change: No specific dosing guidelines provided. ³⁵

Dose:
Patients > 28 kg ³⁵:
Week 1: 17 mg 3 times daily
Week 2: 33 mg 3 times daily
Week 3: 67 mg 3 times daily
Week 4: 133 mg 3 times daily
Week 5 and beyond: 200 mg 3 times daily

Patients < 28 kg ³⁶:
Week 1: 0.66 mg/kg 3 times daily
Week 2: 1.33 mg/kg 3 times daily
Week 3: 2.66 mg/kg 3 times daily
Week 4: 4.66 mg/kg 3 times daily
Week 5 and beyond: 7 mg/kg 3 times daily

Metabolized by multiple hepatic enzymes (CYP and UGT). ³⁵ Ganaxolone AUC increased 1.1-fold, 1.5-fold, and 3.7-fold in patients with mild, moderate, and severe hepatic impairment, respectively. ³⁵

Lacosamide

Dose: Reduce daily dose by 25%. ²
Maximum recommended daily dose for patients with mild to moderate cirrhosis is 300 mg. ¹¹
Patients should be observed closely for adverse reactions. Dose initiation and titration should be directed by clinical response and tolerability.

Not recommended ²

Excreted unchanged in the urine (30 %) and metabolized by CYP2C9, CYP2C19, and CYP3A4. ¹¹ 60% higher AUC in healthy volunteers with moderate hepatic impairment (Child-Pugh Grade B). ² The pharmacokinetics of lacosamide have not been studied in patients with severe liver disease. ¹¹

Child-Pugh Grade A

Child-Pugh Grade B

Child-Pugh Grade C

Lamotrigine

No change: No dose reduction³⁷

Dose: Decrease lamotrigine initial, escalation, and daily dose by ~25%³⁷

Dose: In patients with severe liver impairment without ascites, decrease lamotrigine initial, escalation, and daily doses by ~25%. In patients with severe liver impairment with ascites, decrease lamotrigine initial, escalation, and daily doses by ~50%.³⁷

Metabolized by UGT1A4 and other UGTs.¹¹ Lamotrigine AUC increased 1.1-fold, 1.5-fold, and 3.7-fold in patients with mild, moderate, and severe hepatic impairment, respectively.³⁸ In patients with Gilbert's syndrome, lamotrigine doses should be reduced by one third.¹¹

Levetiracetam

No change: No dose adjustment³⁹

No change: No dose adjustment³⁹

Eliminated primarily by renal excretion of unchanged drug (66%) and by amide-mediated hydrolysis.¹¹ Levetiracetam AUC was not altered in patients with mild hepatic failure (Child-Pugh A) and increased 1.1-fold and 2.6-fold in moderate and severe hepatic failure (Child-Pugh B and C), respectively.³⁸ Accordingly, the dose was suggested to be reduced by 50% in patients with severe hepatic impairment.⁴⁰ However, because decreased renal clearance accounted for most of the reduction, no dose adjustment is required.³⁹

Oxcarbazepine

No change: No specific dosing guidelines provided.⁴¹

Not recommended: Data are not available for severe impairment of hepatic function.

A pro-drug that is converted to its active metabolite, monohydroxy derivative (MHD). MHD is renally excreted unchanged (30 %) or metabolized by UGTs.¹¹ MHD pharmacokinetics are not affected by mild or moderate hepatic impairment, in line with the lack of effect on other UGT-metabolized drugs.¹¹

Perampanel

Dose: Starting dose 2 mg once daily. Increase dosage by increments of 2 mg once daily no more frequently than every 2 weeks. Maximum daily dose 6 mg.⁴²

Not recommended⁴²

Perampanel is eliminated by CYP3A4 metabolism and renal excretion of unchanged drug. Perampanel AUC increased 1.5-fold and 2.6-fold in patients with mild and moderate hepatic impairment, respectively. Pharmacokinetics were not studied in patients with severe hepatic dysfunction.⁴²

Child-Pugh Grade A

Child-Pugh Grade B

Child-Pugh Grade C

Phenobarbital

No change / Dose: A "last resort" ASM. ³ No specific recommendation on dose adjustment in labeling. ⁴³ A 50 % reduction in dose may be required in patients with moderate to severe hepatic cirrhosis. ¹¹ Should be avoided if possible in patients with new-onset acute hepatic dysfunction. ¹¹

Longer half-life in patients with cirrhosis compared with healthy controls; no difference in patients with active hepatitis. ^{11,44}

Phenytoin and fosphenytoin

Dose / Not recommended: A "last resort" ASM. ³ Should be avoided in patients with new-onset acute hepatic dysfunction. ¹¹ Patients with a history of liver disease should not receive the oral loading regimen. ⁴⁵ In patients with renal or hepatic disease, the monitoring of unbound phenytoin concentrations may be more relevant. ⁴⁵ Fosphenytoin may need to be administered at lower doses or infused more slowly. ⁴⁶ In patients with acute hepatotoxicity, fosphenytoin should be immediately discontinued and not re-administered. ⁴⁷

No significant effect of acute viral hepatitis on phenytoin oral clearance; a small effect on phenytoin protein binding. ⁴⁸ A special concern in patients with hypoalbuminemia. ³ Based on studies with sensitive CYP substrates, considerable decrease in the activity of CYP2C19 in mild, moderate, and severe hepatic cirrhosis; ¹⁶⁻¹⁸ a milder decrease in CYP2C9 activity in patients with severe cirrhosis. ^{11,19} Non-linear pharmacokinetics. Decreased CYP2C19 activity among pediatric patients (12-21 YO) with NASH (71% decrease in omeprazole metabolic ratio). ²⁰

Pregabalin

No change: No specific dosing guidelines provided. ⁴⁹

No change / Dose: No specific dosing guidelines provided. ⁴⁹ No change, but if hepatorenal syndrome is present, dose reduction and increase in frequency would be required in renal impairment.

Negligible metabolism and excretion in urine as unchanged drug. ⁴⁹ The pharmacokinetics of pregabalin have not been formally studied in patients with liver disease. ⁵⁰

Primidone

No specific recommendation in product information. ⁵¹ See phenobarbital

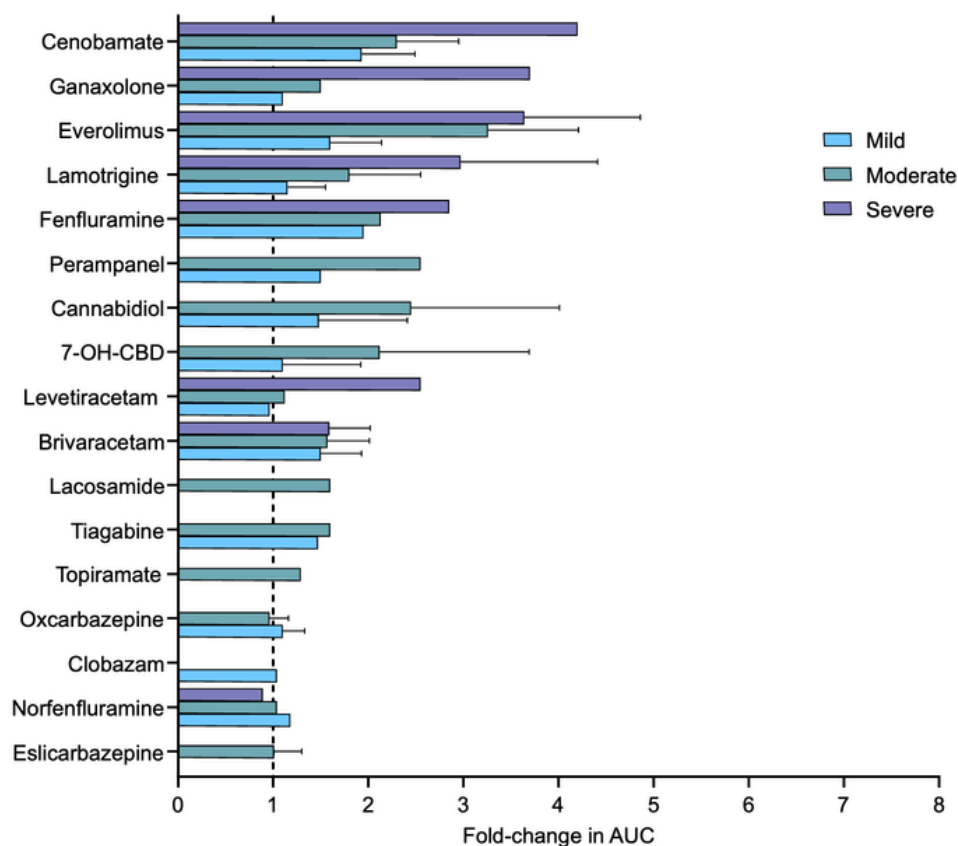
No Comment

Child-Pugh Grade A		Child-Pugh Grade B	Child-Pugh Grade C
Rufinamide			
	No change specified, but use with caution: Caution should be exercised in treating patients with mild (Child-Pugh score 5 to 6) to moderate (Child-Pugh score 7 to 9) hepatic impairment. ³⁶ Use with caution.		Not recommended: Use in patients with severe hepatic impairment (Child-Pugh score 10 to 15) is not recommended. ³⁶
No published studies evaluated the pharmacokinetics of rufinamide in patients with hepatic dysfunction. ¹¹			
Stiripentol			
	No change : No dose adjustment specified. ⁵²	Not recommended: Because stiripentol is mainly metabolized by hepatic oxidation and UGT conjugation, administration to patients with moderate or severe liver impairment is not recommended. ^{11,52}	
There has been no formal study of the pharmacokinetics of stiripentol in patients with liver impairment. ^{11,52}			
Tiagabine			
	Dose: Reduced initial and maintenance doses of tiagabine and/or longer dosing intervals required. ²⁴		Not Recommended
Unbound concentrations and free fractions increase with hepatic impairment. ⁵³ In patients with moderate hepatic impairment (Child-Pugh score B), clearance of unbound drug is reduced by about 60%. ²⁴			
Valproic acid and its derivatives (valproic acid, sodium valproate, and divalproex sodium) Sara			
	Contraindicated A “last resort” ASM. ³ Contraindicated in patients with hepatic disease or significant hepatic dysfunction, ⁵⁶ in particular in new-onset acute hepatic dysfunction. ¹¹ The disease or extent of dysfunction are not defined in labeling. Literature suggests caution in valproate use in patients with hepatic disease; in moderate to severe cirrhosis, dosage should be reduced by at least 50 %. Monitoring valproate using total plasma concentrations may underestimate unbound and lead to overdosage; since valproate unbound concentrations are not routinely available to caregivers, patients should be closely monitored clinically for signs of valproate toxicity. ¹¹		Contraindicated Should be discontinued immediately in the presence of significant hepatic dysfunction. ⁵⁶
High hepatotoxicity potential. 50% decrease in clearance reported in patients with cirrhosis. Larger unbound fractions (2 to 2.6-fold increase) due to decreased albumin concentrations. ^{56,57} Metabolism may be shifted to alternate pathways with the production of hepatotoxic metabolites. ³			

Child-Pugh Grade A		Child-Pugh Grade B	Child-Pugh Grade C
Vigabatrin			
	No change No specific dosing guidelines provided. ⁵⁸		
Excreted renally without metabolism. ¹¹ Vigabatrin pharmacokinetics have not been formally studied in patients with hepatic disease. ⁵⁸			
Zonisamide			
	Dose: Patients with renal or hepatic disease should be treated with caution. Slower titration and more frequent monitoring might be required. ⁵⁹ Dosage adjustment may be needed in patients with moderate to severe cirrhosis. ¹¹		
Zonisamide is metabolized by CYP3A4 (50%) and NAT2 (20 %). The remainder is renally excreted unchanged (15–30 %). ¹¹ The pharmacokinetics of zonisamide have not been studied in patients with impaired liver function. ⁵⁹ Mild Liver cirrhosis is predicted to have a minimal effect.			
Diazepam			
	No change / Dose: Diazepam rectal gel and injection should be used with caution in patients with liver disease. ^{60,61} No special precautions are listed in the FDA product information for diazepam nasal spray. ⁶² A dose reduction is needed in patients with all stages of hepatic cirrhosis. ⁶¹		
Use of benzodiazepines may worsen hepatic encephalopathy. ⁶³ Metabolized by CYP2C19 and CYP3A4. ¹¹ Following intravenous administration, the clearance of diazepam decreases by half, and the half-life is prolonged 2-5-fold in patients with alcoholic cirrhosis compared with age-matched control subjects. ^{61,64} Similar decreases in clearance were found in patients with mixed cirrhosis and viral hepatitis. ¹¹			
Lorazepam			
	No change but caution required No specific dosing guidelines provided. Caution required. ⁶³	Dose: In patients with severe hepatic insufficiency and/or encephalopathy. ⁶³	
Use of benzodiazepines may worsen hepatic encephalopathy. ⁶³ Metabolized by UGT2B15. ¹¹ Cirrhosis associated with a 2-fold increase in the mean elimination half-life (due to a similar increase in the volume of distribution, without a change in clearance). No significant changes in the kinetics of lorazepam in patients with acute viral hepatitis. ⁶⁵ In patients with Gilbert's syndrome, doses should be reduced by one third. ¹¹			
Midazolam			
	Dose: Doses should be significantly decreased in patients with hepatic dysfunction. ¹¹ No special precaution listed for midazolam in 0.9% sodium chloride ⁶		
Use of benzodiazepines may worsen hepatic encephalopathy. ⁶³ A prototypic CYP3A substrate. ²⁸ In patients with mild to moderate cirrhosis treated with an intravenous dose, decreased clearance and greater sedation. ¹¹			

AUCR, ratio of AUC values in the presence of hepatic dysfunction/normal hepatic function. CmaxR, ratio of Cmax values in the presence of hepatic dysfunction/normal hepatic function. IV, intravenously; NAFL, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NASH-WC, NASH without cirrhosis; NAT, N-acetyltransferase; NET, neuroendocrine tumors; RCC, renal cell carcinoma; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis complex.

FIGURE 1. EFFECT OF HEPATIC DYSFUNCTION ON EXPOSURE TO ANTIEPILEPTIC MEDICATIONS.



Change in exposure is expressed as the ratio of the area under the concentration-time curve of the antiepileptic medication in the absence or presence of impaired hepatic function. Values are shown as geometric mean ratios with 90% confidence intervals (error lines; 95% for eslicarbazepine) or ratio of the means (no error lines). A ratio of 1 (vertical line) indicates no change in exposure. The data of oxcarbazepine refer to its active metabolite, licarbazepine. Also shown are the active metabolites of cannabidiol (7-OH-CBD) and fenfluramine (norfenfluramine).

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