09/2025

Epidiolex
אפידיולקס

CANNABIDIOL 100MG/1ML
Solution

רופא/ה, רוקח/ת נכבד/ה,
חברת ניאופרם בע"מ מבקשת להודיע על עדכון העלונים לרופא ולצרכן של התכשיר שבנדון. העלונים עודכנו בתאריך 09/2025.

ההתוויה הרשומה כיום בישראל לתכשיר:

Epidiolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older.

מקראה לעדכונים המסומנים:
מידע שהוסר -מסומן בקו אדום חוצה ~~XXX~~
תוספת -כתב **כחול**
טקסט שזז מקום ירוק

להלן מתוארים העדכונים העיקריים בעלונים לרופא ולצרכן, בעלונים קיימים עדכונים נוספים.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on EPIDIOLEX

Strong CYP3A4 or CYP2C19 Inducers

Concomitant use~~Coadministration~~ with a strong CYP3A4 and CYP2C19 inducer (rifampin 600 mg once daily) decreased cannabidiol and 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 (11.3)]*. Consider an increase in EPIDIOLEX dosage (based on clinical response and tolerability) up to 2-fold, when concomitantly used~~coadministered~~ with a strong CYP3A4 and/or CYP2C19 inducer.

7.2 Effect of EPIDIOLEX on Other Drugs

~~UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 Substrates~~

~~Cannabidiol is a weak inhibitor of CYP1A2 *[see Clinical Pharmacology (11.3)]*. Increases in exposure of sensitive CYP1A2 substrates (e.g., caffeine, theophylline, or tizanidine) may be observed when coadministered with cannabidiol.~~

~~In vitro data predict drug-drug interactions with CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5'-diphospho-glucuronosyltransferase 1A9 (UGT1A9) substrates (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 substrates (e.g., gemfibrozil, lamotrigine, morphine, lorazepam) when coadministered with EPIDIOLEX. Coadministration of EPIDIOLEX is also predicted to cause clinically significant interactions with CYP2C8 and CYP2C9 (e.g., phenytoin) substrates. Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of UGT1A9, UGT2B7, CYP1A2, CYP2C8, and CYP2C9, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX. Because of the potential for both induction and inhibition of enzyme activity, consider adjusting dosage of substrates of CYP2B6, as clinically appropriate.~~

~~Sensitive CYP2C19 Substrates~~

~~In vivo data show that coadministration of EPIDIOLEX increases plasma concentrations of drugs that are metabolized by (i.e., are substrates of) CYP2C19 (e.g., diazepam) and may increase the risk of adverse reactions with these substrates *[see Clinical Pharmacology (11.3)]*. Consider a reduction in dosage of sensitive CYP2C19 substrates, as clinically appropriate, when coadministered with EPIDIOLEX.~~

Antiepileptic Drugs

Clobazam

Concomitant use~~Coadministration~~ of EPIDIOLEX ~~produces a 3-fold~~with clobazam increase~~s~~ ~~in~~ plasma concentrations of N-desmethylclobazam, the active metabolite of clobazam *[see Clinical Pharmacology (11.3)]* ~~(a substrate of CYP2C19), with no effect on clobazam levels *[see Clinical Pharmacology (11.3)]*. The~~which ~~increase in N-desmethylclobazam~~ may increase the risk of clobazam-related adverse reactions *[see Adverse Reactions (6) 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~~coadministered~~ with EPIDIOLEX.

Stiripentol

Concomitant use of EPIDIOLEX ~~and~~ with stiripentol ~~causes an elevation~~increases plasma ~~in~~ exposure~~s~~ ~~to~~ of stiripentol *[see Clinical Pharmacology (11.3)]*. ~~The mechanism of this interaction has not been determined. The clinical relevance of this effect is unknown, but patients should be m~~Monitor~~ed~~ for stiripentol-related adverse ~~drug~~ reactions when concomitantly used with EPIDIOLEX.

Orally Administered P-gp Substrates~~Sensitive P-gp Substrates Given Orally~~

Concomitant use~~Coadministration~~ of EPIDIOLEX with orally administered everolimus~~, a P-gp and CYP3A4 substrate,~~ results in an approximately 2.5-fold increase in plasma exposures~~mean C_{max} and AUC~~ of everolimus *[see Clinical Pharmacology (11.3)]*. 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~~When initiating~~ everolimus ~~in patients taking a stable dosage of EPIDIOLEX,~~ at a lower starting dosage and titrate the dose based on~~dose of everolimus is recommended, with~~ therapeutic drug monitoring.

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

~~UGT1A9, UGT2B7,~~ CYP1A2, CYP2B6, CYP2C8, CYP2C19, and ~~CYP2C19~~UGT1A9 Substrates

CYP1A2 Substrates

Cannabidiol is a weak inhibitor of CYP1A2 *[see Clinical Pharmacology (11.3)]*. Increases in exposure of ~~sensitive~~certain CYP1A2 substrates (e.g., ~~caffeine,~~ theophylline, ~~or~~ tizanidine) may be observed when concomitantly used~~coadministered with cannabidiol~~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.

~~In vitro data predict drug-drug interactions with CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5'-diphospho-glucuronosyltransferase 1A9 (UGT1A9) substrates (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 substrates (e.g., gemfibrozil, lamotrigine, morphine, lorazepam) when coadministered with EPIDIOLEX. Coadministration of EPIDIOLEX is also predicted to cause clinically significant interactions with CYP2C8 and CYP2C9 (e.g., phenytoin) substrates. Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of UGT1A9, UGT2B7, CYP1A2, CYP2C8, and CYP2C9, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX. Because of the potential for both induction and inhibition of enzyme activity, consider adjusting dosage of substrates of CYP2B6, as clinically appropriate.~~

~~*Sensitive* CYP2C19 Substrates~~

Cannabidiol is a moderate inhibitor of CYP2C19 *[see Clinical Pharmacology (11.3)]*. Concomitant use of EPIDIOLEX~~In vivo data show that coadministration of EPIDIOLEX~~ increases plasma concentrations of ~~drugs that are metabolized by (i.e., are substrates of)~~ CYP2C19 substrates ~~(e.g., diazepam)~~ and may increase the risk of adverse reactions ~~with these substrates [see Clinical Pharmacology (11.3)]~~. Consider a dosage reduction ~~in dosage of sensitive~~ CYP2C19 substrates, as clinically appropriate, when concomitantly used~~coadministered~~ 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.

11.3 Pharmacokinetics

(…)

Drug Interaction Studies~~*In Vitro Assessment of Drug Interactions*~~

~~Drug Metabolizing Enzymes *[see Drug Interactions (7.1, 7.2)]*~~

~~Cannabidiol is a substrate for CYP3A4 and CYP2C19. Cannabidiol has the potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations.~~

~~Cannabidiol may induce or inhibit CYP2B6 at clinically relevant concentrations.~~

~~Cannabidiol inhibits uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes UGT1A9 and UGT2B7, but does not inhibit the 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 In Vivo Assessment of Drug Interactions]*.~~

~~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.~~

Clinical Studies and Model-Informed Approaches~~In Vivo Assessment of Drug Interactions~~

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~~volunteers~~ and 20 mg/kg/day in patients).

Coadministration with clobazam in healthy subjects~~volunteers~~ 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 ~~a~~ healthy ~~volunteer trial~~ 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 ~~the~~ healthy ~~volunteer trial~~ subjects, coadministration with valproate resulted in no clinically relevant changes in exposure to cannabidiol or its major metabolites (cannabidiol C_{max} decreased by 26%; 6-OH-CBD AUC increased by 27%; 7-OH-CBD AUC increased by 22%; 7-COOH-CBD C_{max} and AUC increased by 25% and 32%, respectively).

~~*Effect of EPIDIOLEX on Midazolam*~~

~~Coadministration of EPIDIOLEX with midazolam (a sensitive CYP3A4 substrate) did not result in changes in plasma concentrations of midazolam compared to midazolam administered alone.~~

~~*Effect of EPIDIOLEX on* Stiripentol~~

When EPIDIOLEX was coadministered with stiripentol in ~~a~~ healthy ~~volunteer trial~~ 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)]*.

~~*Effect of EPIDIOLEX on Everolimus*~~

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

~~*Effect of EPIDIOLEX on Caffeine*~~

~~In vivo data from steady-state dosing with cannabidiol (750 mg twice daily) when coadministered 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 when caffeine was administered alone *[see Drug Interactions (7.2)]*.~~

Effect of Other Drugs on EPIDIOLEX

~~*Effect of* CYP3A4 and CYP2C19 *Inducers and* Inhibitors *Coadministered with EPIDIOLEX on Exposure to Cannabidiol.*~~

Coadministration of EPIDIOLEX with ~~potent~~ strong inhibitors of CYP3A4 ~~and~~ or CYP2C19 had the following effects on exposure to cannabidiol and its metabolites. Itraconazole, a strong~~The potent~~ CYP3A4 inhibitor~~, itraconazole~~, 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 ~~the potent~~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 ~~the potent CYP3A4 and CYP2C19 inducing agent~~ 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 ~~moderate~~ 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

~~*Effect of EPIDIOLEX on Caffeine*~~*CYP1A2 Substrates*

Coadministration of EPIDIOLEX~~In vivo data from steady-state dosing with cannabidiol~~ (750 mg twice daily) ~~when coadministered~~ with a single dose of caffeine (200 mg), a sensitive CYP1A2 substrate~~substrate~~, showed increased caffeine exposure by 15% for C_{max} and 95% for AUC compared to ~~when~~ caffeine ~~was~~ 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~~*Effect of EPIDIOLEX on Midazolam*~~

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.

~~*Effect of EPIDIOLEX on Everolimus*~~

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

UGT1A9 Substrates

Coadministration of EPIDIOLEX (7.5 mg/kg twice daily) with a single dose of mycophenolate mofetil (1500 mg), a UGT1A9 substrate, increased mycophenolic acid 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 is a substrate for CYP3A4 and CYP2C19. Cannabidiol has the potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations.~~

Cannabidiol has the potential to inhibit CYP2B6 and CYP2C8, and to induce CYP2B6 at clinically relevant concentrations~~Cannabidiol may induce or inhibit CYP2B6 at clinically relevant concentrations.~~

Cannabidiol does not inhibits uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes ~~UGT1A9 and UGT2B7, but does not inhibit the~~ 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~~In Vivo Assessment of Drug Interactions~~].*

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.

תגובות בין תרופתיות

ספר לרופא או לרוקח אם אתה או ילדך לוקחים, או לקחתם לאחרונה, תרופות אחרות כולל תרופות ללא מרשם רופא ותוספי תזונה. נטילת אפידיולקס עם תרופות מסוימות אחרות עשויה לגרום לתופעות לוואי, או להשפיע על פעולת תרופות אחרות, או להשפיע על פעולת אפידיולקס.

בפרט, ייתכן שהרופא יצטרך לשנות את המינון של אפידיולקס אם אתה נוטל את התרופות הבאות:

- תרופות אחרות לאפילפסיה, כמו קרבמזפין, קלובאזאם, ~~למוטריג'ין~~, לוראזפאם, מידזולאם, ~~פניטואין~~, סטיריפנטול ו-ואלפרואט המשמשות לטיפול בפרכוסים
- mTOR או מעכבי קלצינורין, כמו אברולימוס וטאקרולימוס
- קפאין (תרופה לתינוקות הזקוקים לעזרה בנשימה)
- תיאופילין (תרופה המשמשת לטיפול באסתמה)
- ~~בופרופיון (תרופה המסייעת להפסקת עישון או לטיפול בהשמנת יתר)~~
- אפאבירנז (תרופה המשמשת לטיפול ב-HIV/איידס)
- דיפלוניזל, מורפיום (תרופות המשמשות לטיפול בכאב)
- פרופופול (חומר הרדמה המשמש באנשים שעוברים ניתוח)
- פנופיבראט, גמפיברוזיל (תרופות המשמשות להפחתת כולסטרול/שומנים)
- דיאזפאם (משמשת לטיפול בחרדה)

למידע נוסף יש לעיין בעלונים לרופא ולצרכן המעודכנים אשר נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות.
כמו כן, ניתן לקבל את עלוני התכשיר מודפסים על ידי פניה לבעל הרישום: ניאופרם בע"מ, ת.ד. 7063, פתח תקווה 4917001.
טלפון: 03-9373753, פקס: 03-9373774

בברכה
עוז וולך, רוקח/ת ממונה של בעל הרישום