12.2021

EPIDIOLEX

אפידיולקס

Active ingredient and strength:
CANNABIDIOL 100mg/1ml

חומר פעיל וחוזק:
קנאבידיול 100 מ"ג ל-1 מ"ל

SOLUTION

תמיסה

רופא/ה, רוקח/ת נכבד/ה,
ניאופרם בע"מ שמחה להודיע על עדכון עלונים של התכשיר Epidiolex.

- עלוני התכשיר עודכנו בדצמבר 2021, בהודעה זו מתוארים השינויים העיקריים, בעלונים יתכנו שינויים נוספים.
- מידע בטיחותי חדש מופיע על רקע צהוב, טקסט חדש באדום, טקסט שהוסר בכחול עם קו חוצה.

להלן נוסח ההתוויה המאושר לתכשיר:

EPIDIOLEX is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.
Epidiolex is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) in patients 1 year of age and older.

העדכונים העיקריים בעלון לרופא נעשו בסעיפים הבאים:

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

(…)

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

7.2 Effect of EPIDIOLEX on Other Drugs

(…)

Clobazam

Coadministration of EPIDIOLEX produces a ~~bi-directional pharmacokinetic interaction. A~~ 3-fold increase in plasma concentrations of N-desmethylclobazam, the active metabolite of clobazam (a substrate of CYP2C19~~) can occur along with a 1.5-fold increase in exposure to 7-hydroxy-cannabidiol (7-OH-CBD; an active metabolite of cannabidiol~~), with no effect on clobazam levels *[see Clinical Pharmacology (11.3)]*. The ~~I~~increase~~d~~ in N-desmethylclobazam may ~~systemic levels of these active substances may lead to enhanced pharmacological effects and to an~~ increase ~~in~~ 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 coadministered with EPIDIOLEX.
(…)

Sensitive P-gp Substrates Given Orally
Coadministration of EPIDIOLEX with orally administered everolimus, a P-gp and CYP3A4 substrate, results in an approximately 2.5-fold increase in 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. When initiating everolimus in patients taking a stable dosage of EPIDIOLEX, a lower starting 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 on coadministration with EPIDIOLEX. Therapeutic drug monitoring and dose reduction of other P-gp substrates should be considered when given orally and concurrently with EPIDIOLEX.

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7.3 Concomitant Use of EPIDIOLEX and Valproate

(…)

~~7.4 Concomitant Use of EPIDIOLEX and Mammalian Target of Rapamycin (mTOR) or Calcineurin Inhibitors~~

~~No dedicated drug-drug interaction studies have been conducted with mTOR inhibitors (e.g., everolimus) or calcineurin inhibitors (e.g., tacrolimus). Reports in the literature suggest that cannabidiol administration resulted in increased serum levels of everolimus, sirolimus, or tacrolimus. The mechanism of increase in mTOR or calcineurin inhibitors concentrations is not clearly understood. Consider a reduction in dosage of everolimus, sirolimus, or tacrolimus, if adverse reactions known to occur with those medications are experienced when coadministered with EPIDIOLEX.~~

11 CLINICAL PHARMACOLOGY

11.3 Pharmacokinetics

(…)

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]*.

(…)

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)]*.

12 NONCLINICAL TOXICOLOGY

12.1 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 5 and 3 times that the recommended human doses (RHDs) of 20 and 25 mg/kg/day, respectively.

The carcinogenic potential of cannabidiol has not been assessed in rats.

~~Adequate studies of the carcinogenic potential of cannabidiol have not been conducted.~~

(…)

העדכונים העיקריים בעלון לצרכן נעשו בסעיפים הבאים:

2. לפני שימוש בתרופה

(...)

תגובות בין תרופתיות

(...)

- mTOR או מעכבי קלציונורין, כמו אברולימוס וטאקרולימוס

- העלונים מצורפים להודעתנו להלן
- העלונים נשלחו למשרד הבריאות לצורך העלאתם למאגר התרופות שבאתר משרד הבריאות.
- ניתן לקבל עלונים אלה מודפסים על ידי פניה ישירה לבעל הרישום:
ניאופרם בע"מ, רח' השילוח 6, ת.ד. 7063, פתח תקווה 4917001, טלפון: 03-9373737.

בברכה,
עוז וולך, רוקח ממונה של בעל הרישום