

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

EPIDYOLEX[®] 100 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral solution contains 100 mg cannabidiol.

Excipients with known effect:

Each mL of EPIDYOLEX oral solution contains 79 mg of ethanol absolute, 736 mg sesame oil, and 0.5 mg of sucralose.

For the full list of excipients, see [section 6.1](#).

3. PHARMACEUTICAL FORM

Oral solution

Clear, colourless to yellow solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EPIDYOLEX is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) for patients 2 years of age and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

EPIDYOLEX should be initiated and supervised by a neurologist.

Dose

The recommended starting dose of EPIDYOLEX is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day).

Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk and with adherence to the monitoring schedule (see [section 4.4](#)).

Each EPIDYOLEX carton is supplied with:

- Two 1 mL syringes graduated in 0.05 mL increments (each 0.05 mL increment corresponds to 5 mg EPIDYOLEX)
- Two 5 mL syringes graduated in 0.1 mL increments (each 0.1 mL increment corresponds to 10 mg EPIDYOLEX).

If the calculated dose is 100 mg (1 mL) or less, the smaller 1 mL oral syringe should be used.

If the calculated dose is more than 100 mg (1 mL), the larger 5 mL oral syringe should be used.

The calculated dose should be rounded to the nearest graduated increment.

Discontinuation

EPIDYOLEX may be discontinued for lack of efficacy or tolerability issues. If EPIDYOLEX is to be discontinued, the dose should be decreased gradually. In clinical trials, EPIDYOLEX discontinuation was achieved by reducing the dose by approximately 10% per day for 10 days (see [section 4.4](#)). A slower or faster down titration may be required, as clinically indicated, at the discretion of the prescriber.

Missed doses

In the case of one or more missed doses, the missed doses should not be compensated. Dosing should be resumed at the existing treatment schedule. In the case of more than 7 days' missed doses, re-titration to the therapeutic dose should be made.

Dosage adjustment

Special populations

Elderly

Clinical trials of EPIDYOLEX in the treatment of LGS and DS did not include a sufficient number of patients aged above 55 years to determine whether or not they respond differently from younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other concurrent therapy (see [section 4.4, Hepatocellular injury](#) and [section 5.2](#)).

Renal impairment

EPIDYOLEX can be administered to patients with mild, moderate, or severe renal impairment without dose adjustment (see [section 5.2](#)). There is no experience in patients with end-stage renal disease. It is not known if EPIDYOLEX is dialysable.

Hepatic impairment

EPIDYOLEX does not require dose adjustment in patients with mild hepatic impairment (Child-Pugh A).

Caution should be used in patients with moderate hepatic impairment (Child-Pugh B) and EPIDYOLEX should not be used in patients with severe hepatic impairment (Child-Pugh C), unless the potential benefit outweighs the risk. A lower starting dose is recommended in patients with moderate or severe hepatic impairment. The dose titration should be performed as detailed in the [Table 1](#).

Table 1: Dose adjustments in patients with moderate or severe hepatic impairment

Hepatic Impairment	Starting Dose	Maintenance Dose	Maximum Recommended Dose
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)	2 mg/kg twice daily (4 mg/kg/day)*

*Higher doses of EPIDYOLEX may be considered in patients with severe hepatic impairment where the potential benefits outweigh the risks.

Paediatric population

There is no relevant use of EPIDYOLEX in children aged below 6 months.

The safety and efficacy of EPIDYOLEX in children aged 6 months to 2 years have not yet been established. No data are available.

Dose adjustments of other medicinal products used in combination with EPIDYOLEX

A physician experienced in treating patients who are on concomitant antiepileptic drugs (AEDs) should evaluate the need for dose adjustments of EPIDYOLEX or of the concomitant medicinal product(s) to manage potential drug interactions (see [section 4.4](#) and [section 4.5](#)).

Method of administration

Oral use

Food may increase EPIDYOLEX levels and therefore it should be taken consistently either with or without food, including the ketogenic diet. When taken with food, a similar composition of food should be considered, if possible (see [section 5.2](#)).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance, or to any of the excipients listed in [section 6.1](#).

Patients with transaminase elevations greater than 3 times the upper limit of normal (ULN) and bilirubin greater than 2 times the ULN (see [section 4.4](#)).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Hepatocellular injury

EPIDYOLEX can cause dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) (see [section 4.8](#)). The elevations typically occur in the first two months of treatment initiation; however, there were cases observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate.

In clinical trials, the majority of ALT elevations occurred in patients taking concomitant valproate. Concomitant use of clobazam also increased the incidence of transaminase elevations, although to a lesser extent than valproate. Dose adjustment or discontinuation of valproate or dose adjustment of clobazam should be considered if transaminase elevations occur.

Resolution of transaminase elevations occurred with discontinuation of EPIDYOLEX or reduction of EPIDYOLEX and/or concomitant valproate in about two-thirds of the cases. In about one-third of the cases, transaminase elevations resolved during continued treatment with EPIDYOLEX, without dose reduction.

Patients with baseline transaminase levels above the ULN had higher rates of transaminase elevations when taking EPIDYOLEX. In some patients, a synergistic effect of concomitant treatment with valproate upon baseline elevated transaminases resulted in a higher risk of transaminase elevations.

In an uncontrolled study in patients in a different non-epilepsy indication, 2 elderly patients experienced elevations of alkaline phosphatase levels above 2 times the ULN in combination with transaminase elevations. The elevations resolved after discontinuation of EPIDYOLEX.

Patients with severe hepatic impairment (Child-Pugh C) are to be treated with particular caution. In such patients, the potential benefit must outweigh the risk (see [section 4.2, Hepatic impairment](#)).

Monitoring:

In general, transaminase elevations of greater than 3 times the ULN in the presence of elevated bilirubin without an alternative explanation are an important predictor of severe liver injury. Early identification of elevated transaminase may decrease the risk of a serious outcome. Patients with elevated baseline transaminase levels above 3 times the ULN, or elevations in bilirubin above 2 times the ULN, should be evaluated prior to initiation of EPIDYOLEX treatment.

Prior to starting treatment with EPIDYOLEX, obtain serum transaminases (ALT and AST) and total bilirubin levels.

Routine Monitoring:

Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment with EPIDYOLEX, and periodically thereafter or as clinically indicated.

Upon changes in EPIDYOLEX dose above 10 mg/kg/day or changes in medicinal products (dose change or additions) that are known to impact the liver, this monitoring schedule should be restarted.

Intensified Monitoring:

Patients with identified baseline elevations of ALT or AST and patients who are taking valproate should have serum transaminases and total bilirubin levels obtained at 2 weeks, 1 month, 2 months, 3 months, and 6 months after initiation of treatment with EPIDYOLEX, and periodically thereafter or as clinically indicated.

Upon changes in EPIDYOLEX dose above 10 mg/kg/day or changes in medicinal products (dose change or additions) that are known to impact the liver, this monitoring schedule should be restarted.

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), serum transaminases and total bilirubin should be measured promptly and treatment with EPIDYOLEX should be interrupted or discontinued, as appropriate. EPIDYOLEX should be discontinued in any patients with elevations of transaminase levels greater than 3 times the ULN

and bilirubin levels greater than 2 times the ULN. Patients with sustained transaminase elevations of greater than 5 times the ULN should also have treatment discontinued. Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes. Dosage adjustment should be considered of any co-administered medicinal product that is known to affect the liver (e.g., valproate and clobazam).

Somnolence and sedation

EPIDYOLEX can cause somnolence and sedation, which occur more commonly early in treatment and may diminish with continued treatment. The occurrence was higher for those patients on concomitant clobazam (see [section 4.5](#) and [section 4.8](#)). Other CNS depressants, including alcohol, can potentiate the somnolence and sedation effect.

Withdrawal of antiepileptic drugs (AEDs)

As with most antiepileptic drugs, EPIDYOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus (see [section 4.2](#)). If withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

Increased seizure frequency

As with other AEDs, a clinically relevant increase in seizure frequency may occur during treatment with EPIDYOLEX, which may require adjustment in dose of EPIDYOLEX and/or concomitant AEDs, or discontinuation of EPIDYOLEX, to optimise the benefit-risk balance.

Suicidal behaviour and ideation

Suicidal behaviour and ideation have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials with AEDs has shown a small increased risk of suicidal behaviour and ideation. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for EPIDYOLEX.

Patients should be monitored for signs of suicidal behaviour and ideation and appropriate treatment should be considered. Patients and caregivers of patients should be advised to seek medical advice should any signs of suicidal behaviour and ideation emerge.

Sesame oil in the formulation

This medicinal product contains refined sesame oil which may rarely cause severe allergic reactions.

Use in the elderly

See [section 4.2](#) and [section 5.2](#).

Paediatric use

See [section 4.2](#) and [section 5.2](#).

Administration of cannabidiol to juvenile rats for 10 weeks (PND4-6 [SC] and PND7-77[PO]) resulted in delayed sexual maturation (males), decreased locomotor activity and increased bone mineral density. The lowest dose causing developmental toxicity in juvenile rats (15/100 mg/kg SC/PO) was associated with cannabidiol exposures (based on C_{max}) approximately 20 times that anticipated at the maximum clinical dose.

Effects on laboratory tests

See [section 4.4](#) and [section 4.8](#).

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

CYP3A4 or CYP2C19 inducers

The strong CYP3A4/2C19 inducing agent rifampicin (600 mg administered once daily) decreased plasma concentrations of cannabidiol and of 7-hydroxy-cannabidiol (7-OH-CBD; an active metabolite of cannabidiol) by approximately 30% and 60%, respectively. Other strong inducers of CYP3A4 and/or CYP2C19, such as carbamazepine, enzalutamide, mitotane and St. John's wort, when administered concomitantly with EPIDYOLEX, may also cause a decrease in the plasma concentrations of cannabidiol and of 7-OH-CBD by a similar amount. These changes may result in a decrease in the effectiveness of EPIDYOLEX. Dose adjustment may be necessary.

UGT inhibitors

EPIDYOLEX is a substrate for UGT1A7, UGT1A9 and UGT2B7. No formal drug-drug interaction studies have been conducted with EPIDYOLEX in combination with UGT inhibitors, therefore caution should be taken when co-administering drugs that are known inhibitors of these UGTs. Dose reduction of EPIDYOLEX and/or the inhibitor may be necessary when given in combination.

Concomitant AED treatments

The pharmacokinetics of EPIDYOLEX are complex and may cause interactions with the patient's concomitant AED treatments. EPIDYOLEX and/or concomitant AED treatment should therefore be adjusted during regular medical supervision and the patient should be closely monitored for adverse drug reactions. In addition, monitoring of plasma concentrations should be considered.

The potential for drug-drug interactions with other concomitant AEDs has been assessed in healthy volunteers and patients with epilepsy for clobazam, valproate, stiripentol and everolimus. Although no formal drug-drug interaction studies have been performed for other AEDs, phenytoin and lamotrigine are addressed based on *in vitro* data.

Clobazam

When EPIDYOLEX and clobazam are co-administered, bi-directional pharmacokinetic (PK) interactions occur. Based on a healthy volunteer study, elevated levels (3- to 4-fold) of *N*-desmethyloclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition, with no effect on clobazam levels. In addition, there was an increased exposure to 7-OH-CBD for which plasma area under the curve (AUC) increased by 47% (see [section 5.2](#)). Increased systemic levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions. Concomitant use of EPIDYOLEX and clobazam increases the incidence of somnolence and sedation compared with placebo (see [section 4.4](#) and [section 4.8](#)). Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co-administered with EPIDYOLEX.

Valproate

Concomitant use of EPIDYOLEX and valproate increases the incidence of transaminase enzyme elevations (see [section 4.4](#)). The mechanism of this interaction remains unknown. If clinically significant increases of transaminases occur, EPIDYOLEX and/or concomitant valproate should be

reduced or discontinued in all patients until a recovery of transaminase elevations are observed (see [section 4.4](#)). Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic medicinal products and EPIDYOLEX (see [section 4.4](#)).

Concomitant use of EPIDYOLEX and valproate increases the incidence of diarrhoea and events of decreased appetite. The mechanism of this interaction is unknown.

Stiripentol

When EPIDYOLEX was co-administered with stiripentol in a healthy volunteer trial there was an increase in stiripentol levels of 28% for maximum measured plasma concentration (C_{max}) and 55% for AUC. In patients, however, the effect was smaller, with an increase in stiripentol levels of 17% in C_{max} and 30% in AUC. The clinical importance of these results have not been studied. The patient should be closely monitored for adverse drug reactions.

Phenytoin

Exposure to phenytoin may be increased when it is co-administered with EPIDYOLEX, as phenytoin is largely metabolised via CYP2C9, which is inhibited by cannabidiol *in vitro*. There are no clinical studies formally investigating this interaction. Phenytoin has a narrow therapeutic index, so combining EPIDYOLEX with phenytoin should be initiated with caution and if tolerability issues arise, dose reduction of phenytoin should be considered.

Lamotrigine

Lamotrigine is a substrate for UGT enzymes including UGT2B7 which is inhibited by cannabidiol *in vitro*. There have not been any clinical studies formally investigating this interaction. Lamotrigine levels may be elevated when it is co-administered with EPIDYOLEX.

Everolimus

Co-administration of EPIDYOLEX with the P-gp and CYP3A4 substrate everolimus in a healthy volunteer study led to an increase in everolimus exposure of approximately 2.5-fold for both C_{max} and AUC. The mechanism for this interaction is believed to be inhibition of intestinal P-gp efflux, leading to increased bioavailability of everolimus. The half-life of everolimus was not affected, confirming the lack of systemic inhibitory effects of EPIDYOLEX on P-gp and CYP3A4 activity. When initiating EPIDYOLEX 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 EPIDYOLEX, a lower starting dose of everolimus is recommended, with therapeutic drug monitoring.

Potential for EPIDYOLEX to affect other medicinal products

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

In vivo data from steady-state dosing with cannabidiol (750 mg twice daily) when co-administered 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. These data indicate that cannabidiol is a weak inhibitor of CYP1A2. Similar modest increases in exposure may be observed with other sensitive CYP1A2 substrates (e.g., theophylline or tizanidine). The clinical importance of these findings has not been studied. The patient should be closely monitored for adverse drug reactions.

In vitro data predict drug-drug interactions with CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5' diphospho-glucuronosyltransferase 1A9 (UGT1A9) (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 (e.g., gemfibrozil, morphine, lorazepam) when co-administered with EPIDYOLEX. Co-administration of EPIDYOLEX is also predicted to cause clinically significant interactions with CYP2C8 (repaglinide) and CYP2C9 (e.g., warfarin) substrates.

In vitro data have demonstrated that cannabidiol inhibits CYP2C19, which may cause increased plasma concentrations of medicines that are metabolised by this isoenzyme such as clobazam and omeprazole. Dose reduction should be considered for concomitant medicinal products that are sensitive CYP2C19 substrates or that have a narrow therapeutic index.

Because of potential inhibition of enzyme activity, dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, and CYP2C9 should be considered, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDYOLEX. Because of potential for both induction and inhibition of enzyme activity, dose adjustment of substrates of CYP1A2 and CYP2B6 should be considered, as clinically appropriate.

In vitro assessment of interaction with UGT enzymes

In vitro data suggest that cannabidiol is a reversible inhibitor of UGT1A9 and UGT2B7 -mediated activity at clinically relevant concentrations. The metabolite 7 -carboxy -cannabidiol (7-COOH-CBD) is also an inhibitor of UGT1A1, UGT1A4 and UGT1A6 -mediated activity *in vitro*. Dose reduction of the substrates may be necessary when EPIDYOLEX is administered concomitantly with substrates of these UGTs.

Sensitive P-gp substrates given orally

Co-administration of EPIDYOLEX with orally administered everolimus, a P-gp and CYP3A4 substrate, has shown that intestinal P-gp efflux might be inhibited, as demonstrated by an increase in everolimus bioavailability. Increases in exposure of other orally administered P-gp substrates (e.g., sirolimus, tacrolimus, digoxin) may be observed on co-administration with EPIDYOLEX. Therapeutic drug monitoring and dose reduction of other P-gp substrates should be considered when given orally and concurrently with EPIDYOLEX.

Ethanol in the formulation

Each mL of EPIDYOLEX contains 79 mg of ethanol absolute, equivalent to 10% v/v anhydrous ethanol, i.e., up to 553.04 mg ethanol per maximal single EPIDYOLEX dose (10 mg/kg) for an adult weighing 70 kg (7.9 mg ethanol/kg). For an adult weighing 70 kg, this is equivalent to 14 mL of beer, or 6 mL of wine per dose.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy (Category B2)

There are only limited data from the use of EPIDYOLEX in pregnant women.

The embryo-fetal development (EFD) study performed in rabbits evaluated doses of 50, 80, or 125 mg/kg/day. The dose level of 125 mg/kg/day induced decreased fetal body weights and increased fetal structural variations associated with maternal toxicity. Maternal plasma cannabidiol exposures at the no observed-adverse-effect-level (NOAEL) for EFD toxicity in rabbits were less than that in humans at 20 mg/kg/day.

In rats, the EFD study evaluated doses of 75, 150, or 250 mg/kg/day. Embryofetal mortality was observed at the high dose, with no treatment-related effects on implantation loss at the low or mid doses. The NOAEL was associated with maternal plasma exposures (AUC) approximately 50 times greater than the anticipated exposure in humans at 20 mg/kg/day.

A pre- and post-natal development study was performed in rats at doses of 75, 150, or 250 mg/kg/day. Decreased growth, delayed sexual maturation, behavioural changes (decreased activity), and adverse effects on male reproductive organ development (small testes in adult offspring) and fertility were observed in the offspring at doses \geq 150 mg/kg/day. The NOAEL was associated with maternal plasma cannabidiol exposures approximately 9 times that in humans at 20 mg/kg/day.

As a precautionary measure, EPIDYOLEX should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

Breast-feeding

There are no clinical data on the presence of EPIDYOLEX or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

Studies in animals have shown toxicological changes in lactating animals, when the mother was treated with cannabidiol (see Pregnancy (Category B2): pre- and post-natal rat study findings).

There are no human studies on excretion of EPIDYOLEX in breast milk. Given that cannabidiol is highly protein bound and will likely pass freely from plasma into milk, as a precaution, breast feeding should be discontinued during treatment.

Fertility

No human data on the effect of EPIDYOLEX on fertility are available.

No adverse reactions were observed on male or female fertility or reproduction performance in rats at doses up to 250 mg/kg/day (approximately 60-fold greater than the maximum recommended human dose (MRHD) at 20 mg/kg/day).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

EPIDYOLEX has a major influence on the ability to drive and operate machines because it may cause somnolence and sedation (see [section 4.4](#)). Patients should be advised not to drive or operate machinery unless they are certain of the medicine's effect on their ability to drive or operate machinery. As EPIDYOLEX is a cannabis-based medicine, patients considering driving should also be aware of any local state laws in this respect (see [section 4.8](#)).

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

The most common adverse reactions are somnolence, decreased appetite, diarrhoea, pyrexia, fatigue, and vomiting.

The most frequent cause of discontinuations was transaminase elevation.

Tabulated list of adverse reactions

Adverse reactions reported with EPIDYOLEX in placebo-controlled clinical studies are listed in the [Table 2](#) by System Organ Class and frequency.

The frequencies are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reactions from clinical trials
Infections and infestations	Common	Pneumonia ^a , Bronchitis, Nasopharyngitis, Urinary tract infection
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Increased appetite
Psychiatric disorders	Common	Irritability, Insomnia, Aggression, Abnormal behaviour, Agitation
Nervous system disorders	Very common	Somnolence ^a
	Common	Lethargy, Drooling, Tremor
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very common	Diarrhoea, Vomiting
Hepatobiliary disorders	Common	AST increased, ALT increased, GGT increased, Liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Rash
General disorders and administration site conditions	Very common	Pyrexia, Fatigue
Investigations	Common	Weight decreased

^a Grouped Terms: Pneumonia: Pneumonia, Pneumonia RSV, Pneumonia mycoplasmal, Pneumonia adenoviral, Pneumonia viral, Aspiration pneumonia; Somnolence: Somnolence, Sedation.

Description of selected adverse reactions

Hepatocellular injury

EPIDYOLEX can cause dose-related elevations of ALT and AST (see [section 4.4](#)).

In controlled studies for LGS and DS, the incidence of ALT elevations above 3 times the ULN was 13% in EPIDYOLEX-treated patients compared with 1% in patients on placebo. Less than 1% of EPIDYOLEX-treated patients had ALT or AST levels greater than 20 times the ULN. There were cases of transaminase elevations associated with hospitalisation in patients taking EPIDYOLEX.

Risk Factors for hepatocellular injury

Concomitant Valproate and Clobazam, Dose of EPIDYOLEX and Baseline Transaminase Elevations

Concomitant valproate and clobazam

In EPIDYOLEX-treated patients, the incidence of ALT elevations greater than 3 times the ULN was 23% in patients taking both concomitant valproate and clobazam, 17% in patients taking

concomitant valproate (without clobazam), 3% in patients taking concomitant clobazam (without valproate), and 2% in patients taking neither drug.

Dose

ALT elevations greater than 3 times the ULN were reported in 16% of patients taking EPIDYOLEX 20 mg/kg/day compared with 3% in patients taking EPIDYOLEX 10 mg/kg/day.

Baseline transaminase elevations

In controlled trials (see [section 5.1](#)) in patients taking EPIDYOLEX 20 mg/kg/day, the frequency of treatment-emergent ALT elevations greater than 3 times the ULN was 31% (84% of these were on valproate) when ALT was above the ULN at baseline, compared to 12% (89% of these were on valproate) when ALT was within the normal range at baseline. A total of 5% of patients (all on valproate) taking EPIDYOLEX 10 mg/kg/day experienced ALT elevations greater than 3 times the ULN when ALT was above the ULN at baseline, compared with 3% of patients (all on valproate) in whom ALT was within the normal range at baseline.

Somnolence and sedation

Somnolence and sedation events have been observed in controlled trials with EPIDYOLEX in LGS and DS. The frequency in patients receiving 10 mg/kg/day EPIDYOLEX was 26% and in patients receiving 20 mg/kg/day EPIDYOLEX was 29%, compared to 10% in patients receiving placebo. The rate was higher in a subgroup of patients on concomitant clobazam (40% in EPIDYOLEX-treated patients taking clobazam compared with 14% in EPIDYOLEX-treated patients not on clobazam).

Decreased weight

EPIDYOLEX can cause weight loss. In LGS and DS patients, the decrease in weight appeared to be dose-related, with 19% of patients on EPIDYOLEX 20 mg/kg/day experiencing a decrease in weight $\geq 5\%$, compared to 8% in patients on EPIDYOLEX 10 mg/kg/day. In some cases, the decreased weight was reported as an adverse event (see the [Table 2](#)). Decreased appetite and weight loss may result in slightly reduced height gain. Continuous weight loss/absence of weight gain should be periodically checked to evaluate if EPIDYOLEX treatment should be continued.

Haematologic abnormalities

EPIDYOLEX can cause decreases in haemoglobin and haematocrit. In LGS and DS patients, the mean decrease in haemoglobin from baseline to end of treatment was -0.37 g/dL in EPIDYOLEX-treated patients. A corresponding decrease in haematocrit was also observed, with a mean change of -1.4% in EPIDYOLEX-treated patients.

Twenty-seven percent (27%) of EPIDYOLEX-treated patients developed a new laboratory--defined anaemia during the course of the study (defined as a normal haemoglobin concentration at baseline, with a reported value less than the lower limit of normal at a subsequent time point).

Increases in creatinine

EPIDYOLEX can cause elevations in serum creatinine. The mechanism has not been determined. In controlled studies in healthy adults and in patients with LGS and DS, an increase in serum creatinine of approximately 10% was observed within 2 weeks of starting EPIDYOLEX. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS and DS.

Pneumonia

Pneumonia has been observed in controlled trials of LGS and DS with clobazam (14% in patients receiving 10 mg/kg/day CBD, 7% in patients receiving 20 mg/kg/day CBD, and 1% receiving placebo) and without concomitant clobazam (0% in patients receiving 10 mg/kg/day CBD, 3% in patients receiving 20 mg/kg/day CBD, and 2% receiving placebo).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://pophealth.my.site.com/carmreportnz/s/>.

4.9 OVERDOSE

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

Symptoms

Experience with doses higher than the recommended therapeutic dose is limited. Mild diarrhoea and somnolence have been reported in healthy adult subjects taking a single dose of 6000 mg; this equates to a dose of over 85 mg/kg for a 70 kg adult. These adverse reactions resolved upon study completion.

Management of overdose

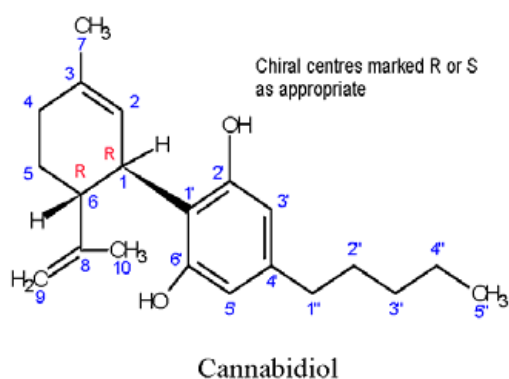
In the event of overdose the patient should be observed and appropriate symptomatic treatment given, including monitoring of vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX24.

Chemical structure



CAS number

13956-29-1

Mechanism of action

The precise mechanisms by which cannabidiol exerts its anticonvulsant effects in humans are unknown. Cannabidiol does not exert its anticonvulsant effect through interaction with cannabinoid receptors. Cannabidiol reduces neuronal hyper-excitability through modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid 1 (TRPV-1) channels, as well as modulation of adenosine-mediated signalling through inhibition of adenosine cellular uptake via the equilibrative nucleoside transporter 1 (ENT-1).

Pharmacodynamic effects

In patients, there is a potential additive anticonvulsant effect from the bi-directional pharmacokinetic interaction between cannabidiol and clobazam, which leads to increases in circulating levels of their respective active metabolites, 7-OH-CBD (approximately 1.5-fold) and N-CLB (approximately 3-fold) (see [section 4.5](#) and [section 5.2](#)).

Clinical efficacy and safety

Adjunctive therapy in patients with LGS

The efficacy of EPIDYOLEX for the adjunctive therapy of seizures associated with LGS was evaluated in two randomised, double-blind, placebo-controlled, parallel-group studies (GWPCARE3 and GWPCARE4). In both studies, patients were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. Each study consisted of a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures (≥ 2 drop seizures per week), a 2-week titration period and a 12-week maintenance period. Mean age of the study population was 15 years and 94% were taking 2 or more concomitant AEDs (cAEDs) during the trial. The most frequently used cAEDs ($>25\%$) in GWPCARE3 and GWPCARE4 were clobazam (mean 49%), valproate (mean 39%), lamotrigine (mean 33%), levetiracetam (mean 32%), and rufinamide (mean 28%).

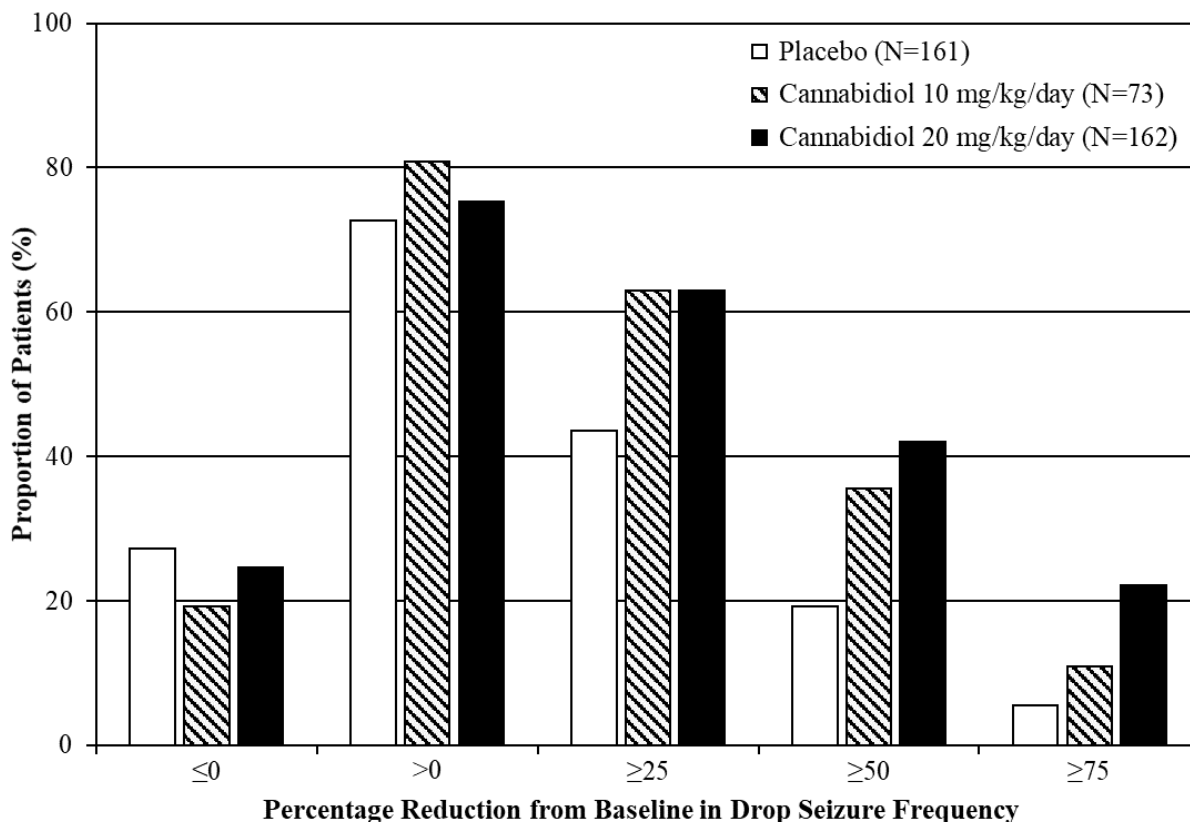
The primary endpoint was the percentage change from baseline in drop seizures per 28 days over the treatment period for the EPIDYOLEX group compared to placebo. Drop seizures were defined as atonic, tonic, or tonic-clonic seizures that led or could have led to a fall or injury. Key secondary endpoints were the proportion of patients with at least a 50% reduction in drop seizure frequency, the percentage change from baseline in total seizure frequency, and Subject/Caregiver Global Impression of Change at the last visit. These outcome measures are summarised in [Table 3](#) and [Figure 1](#).

Table 3: Primary and key secondary outcome measures in LGS studies

	Study GWPCARE3			Study GWPCARE4	
	EPIDYOLEX 20 mg/kg/day (n=76)	EPIDYOLEX 10 mg/kg/day (n=73)	Placebo (n=76)	EPIDYOLEX 20 mg/kg/day (n=86)	Placebo (n=85)
<i>Primary endpoint – Percentage reduction in drop seizure frequency</i>					
<i>Drop seizures</i> Median % Reduction	41.9	37.2	17.2	43.9	21.8
<i>Comparison to Placebo</i>					
Difference	21.6	19.2		17.2	
95% CI	6.7; 34.8	7.7; 31.2		4.1; 30.3	
P-value	0.005	0.002		0.014	
<i>Key Secondary endpoints</i>					
<i>50% responder proportion ^a</i> P-value	39.5 % 0.001	35.6% 0.003	14.5%	44.2% 0.004	23.5%
<i>Total seizures</i> Median % Reduction	38.4	36.4	18.5	41.2	13.7
<i>Comparison to Placebo</i>					
Difference	18.8	19.5		21.1	
95% CI	4.4; 31.8	7.5; 30.4		9.4; 33.3	
P-value	0.009	0.002		0.001	
<i>Mean S/CGIC results (last visit)</i> P-value	3.2 (sl. improved) 0.044	3.0 (sl. improved) 0.002	3.6 (no change)	3.0 (sl. improved) 0.001	3.7 (no change)

CI = 95% confidence interval; Difference = treatment difference (12 weeks); ^a = proportion of patients with at least 50% reduction in drop seizure frequency; sl. = slightly.

Figure 1: Cumulative Proportion of Patients by Category of Seizure Response in the Treatment Period for EPIDYOLEX and Placebo in Patients with Lennox-Gastaut Syndrome (GWPCARE3 and 4)



Compared with placebo, EPIDYOLEX was associated with an increase in the number of drop seizure-free days during the treatment period in each trial, equivalent to an additional 3.3 days per 28 days (10 mg/kg/day) and 2.7 to 4.6 days per 28 days (20 mg/kg/day).

Adjunctive Therapy in patients with DS

The efficacy of EPIDYOLEX for the adjunctive therapy of seizures associated with DS was evaluated in two randomised, double-blind, placebo-controlled, parallel-group studies (GWPCARE2 and GWPCARE1). Each study consisted of a 4-week baseline period, a 2-week titration period and a 12-week maintenance period. Mean age of the study population was 9 years and 94% were taking 2 or more cAEDs during the trial. The most commonly used cAEDs (>25% of patients) in both trials were valproate, clobazam, stiripentol, and levetiracetam.

The primary endpoint was the change in convulsive seizure frequency during the treatment period (Day 1 to the end of the evaluable period) compared to baseline (GWPCARE2), and the percentage change from baseline in convulsive seizures per 28 days over the treatment period (GWPCARE1) for the EPIDYOLEX groups compared to placebo. Convulsive seizures were defined as atonic, tonic, clonic, and tonic-clonic seizures. Key secondary endpoints for GWPCARE2 were the proportion of patients with at least a 50% reduction in convulsive seizure frequency, the change in total seizure frequency, and Caregiver Global Impression of Change at the last visit. The key secondary endpoint for GWPCARE1 was the proportion of patients with at least a 50% reduction in convulsive seizure frequency. These outcome measures are summarised in [Table 4](#) and [Figure 2](#).

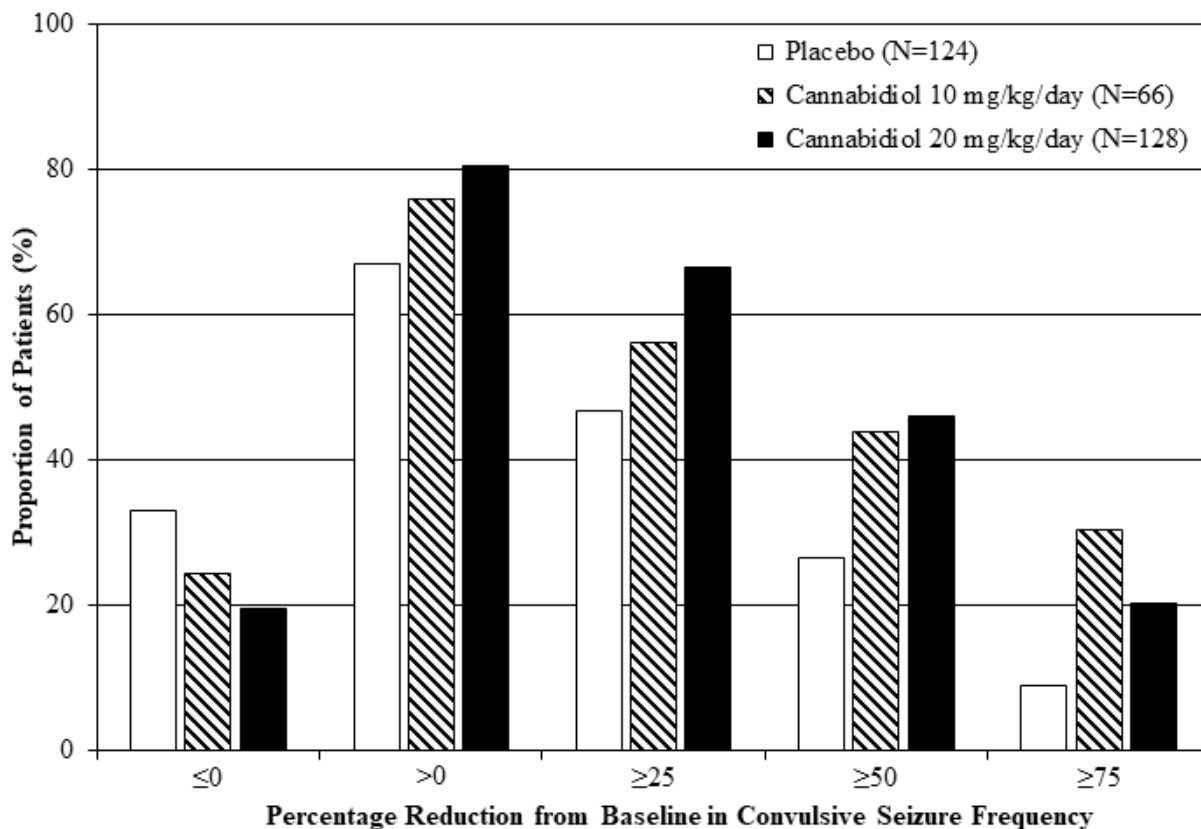
Table 4: Primary and key secondary outcome measures in DS studies

	Study GWPCARE2			Study GWPCARE1	
	EPIDYOLEX 20 mg/kg/day (n=67)	EPIDYOLEX 10 mg/kg/day (n=66)	Placebo (n=65)	EPIDYOLEX 20 mg/kg/day (n=61)	Placebo (n=59)
Primary endpoint –	Reduction in convulsive seizure frequency			Percentage reduction in convulsive seizure frequency	
Convulsive seizures Median % Reduction/ % Reduction	45.7	48.7	26.9	38.9	13.3
Comparison to Placebo					
% Reduction	25.7	29.8			
Difference				22.8	
95% CI	2.9; 43.2	8.4; 46.2		5.4; 41.1	
P-value	0.030	0.010		0.012	
Key Secondary endpoints					
50% responder proportion ^a	49.3%	43.9%	26.2%	42.6%	27.1%
P-value	0.007	0.033		0.078	
Total seizures Median % Reduction/ % Reduction	47.3	56.4	29.7	*	
Comparison to Placebo					
% Reduction					
Difference	25.1	38.0			
95% CI	3.5; 41.9	20.1; 51.9			
P-value	0.026	<0.001			
Mean S/CGIC results (last visit)	3.1	2.8	3.6	*	
P-value	(sl. improved) 0.028	(sl. improved) 0.001	(no change)		

CI= 95% confidence interval; Difference= treatment difference (12 weeks); ^a= proportion of patients with at least 50% reduction in convulsive seizure frequency; sl.=slightly.

* For study GWPCARE1, total seizures and CGIC endpoints were not included in formal hypothesis testing and hence results are not shown.

Figure 2: Cumulative Proportion of Patients by Category of Seizure Response in the Treatment Period for EPIDYOLEX and Placebo in Patients with Dravet Syndrome (GWPCARE2 and 1)



Compared with placebo, EPIDYOLEX was associated with an increase in the number of convulsive seizure-free days during the treatment period in each trial, equivalent to 2.4 days per 28 days (10 mg/kg/day) and 1.3 to 1.4 days per 28 days (20 mg/kg/day).

Adult population

The DS population in studies GWPCARE2 and GWPCARE1 was predominantly paediatric patients, with only 5 adult patients who were 18 years old (1.6%), and therefore limited efficacy and safety data were obtained in the adult DS population.

Dose response

Given that there was no consistent dose response between 10 mg/kg/day and 20 mg/kg/day in the LGS and DS studies, EPIDYOLEX should be titrated initially to the recommended maintenance dose of 10 mg/kg/day (see [section 4.2](#)). In individual patients, titration up to a maximum dose of 20 mg/kg/day may be considered, based on the benefit-risk (see [section 4.2](#)).

Treatment with clobazam

Based on the results of exploratory subgroup analyses there may be additive anticonvulsant effects of EPIDYOLEX in the presence of clobazam, associated with an increased risk of somnolence and sedation and hepatocellular injury (see [section 4.4](#), [section 4.5](#) and [section 4.8](#)).

The concomitant use of EPIDYOLEX and clobazam requires individualised clinical benefit/risk assessment and potential dose adjustments of either or both medicines based on efficacy, tolerability, and safety.

Open-label data

Across both randomised LGS studies, 99.5% of patients who completed the studies were enrolled into the long-term open-label extension study (GWPCARE5). In this study, for patients with LGS treated for 37 to 48 weeks (N=299), the median percentage reduction from baseline in drop seizure frequency was 55% during Week 1–12, which was maintained through to Week 37-48 (60% reduction).

Across both randomised DS studies, 97.7% of patients who completed the studies were enrolled into GWPCARE5. In this study, for patients with DS treated for 37 to 48 weeks (N=214), the median percentage reduction from baseline in convulsive seizure frequency was 56% during Week 1-12, which was maintained through to Week 37-48 (45% reduction).

Abuse

The non-clinical assessment of abuse potential shows that cannabidiol does not produce cannabinoid-like behavioural responses, including generalisation to delta-9-tetrahydrocannabinol (THC) in a drug discrimination study. Cannabidiol also does not produce animal self-administration, suggesting it does not produce rewarding effects and does not result in physical dependence or withdrawal syndrome.

In a human abuse potential study, acute administration of EPIDYOLEX to non-dependent adult recreational drug users at therapeutic and higher doses of 750, 1500, and 4500 mg in the fasted state produced responses above placebo on positive subjective measures such as Drug Liking and Take Drug Again that were within the range usually considered acceptable. In contrast, 10 and 30 mg of dronabinol (synthetic THC) and 2 mg alprazolam produced large increases on positive subjective measures compared to placebo that were statistically significantly greater than those produced by cannabidiol. Compared to dronabinol and alprazolam, EPIDYOLEX has a low abuse potential.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

EPIDYOLEX appears rapidly in plasma with a time to maximum plasma concentration of 2.5-5 hours at steady-state.

Steady -state plasma concentrations are attained within 2-4 days of twice daily dosing based on pre-dose (C_{trough}) concentrations. The rapid achievement of steady state is related to the multiphasic elimination profile of the drug in which the terminal elimination represents only a small fraction of the drug's clearance.

In healthy volunteer studies, co-administration of EPIDYOLEX (750 or 1500 mg) with a high -fat/high calorie meal increased the rate and extent of absorption (5-fold increase in C_{max} and 4-fold increase in AUC) and reduced the total variability of exposure compared with the fasted state in healthy volunteers. Although the effect is slightly smaller for a low-fat/low-calorie meal, the elevation in exposure is still marked (C_{max} by 4-fold, AUC by 3-fold). Furthermore, taking cannabidiol with bovine milk enhanced exposure by approximately 3-fold for C_{max} and 2.5-fold for AUC. Taking cannabidiol with alcohol also caused enhanced exposure to cannabidiol, with a 63% greater AUC.

To minimise the variability in the bioavailability of cannabidiol in the individual patient, administration of EPIDYOLEX should be standardised in relation to food intake including a ketogenic diet (high fat meal) i.e., EPIDYOLEX should be taken consistently with or without food. When taken with food, a similar composition of food should be considered, if possible.

Distribution

In vitro, >94% of cannabidiol and its phase I metabolites were bound to plasma proteins, with preferential binding to human serum albumin.

The apparent volume of distribution after oral dosing was high in healthy volunteers at 20,963 L to 42,849 L and greater than total body water, suggesting a wide distribution of EPIDYOLEX.

Biotransformation

The half-life of cannabidiol in plasma was 56-61 hours after twice daily dosing for 7 days in healthy volunteers.

Cannabidiol is extensively metabolised by the liver via CYP450 enzymes and the UGT enzymes. The major CYP450 isoforms responsible for the phase I metabolism of cannabidiol are CYP2C19 and CYP3A4. The UGT isoforms responsible for the phase II conjugation of cannabidiol are UGT1A7, UGT1A9, and UGT2B7.

Studies in healthy subjects showed there were no major differences in the plasma exposure to cannabidiol in CYP2C19 intermediate and ultra-rapid metabolisers when compared to extensive metabolisers.

The phase I metabolites identified in standard *in vitro* assays were 7-COOH-CBD, 7-OH-CBD, and 6-OH -CBD (a minor circulating metabolite). After multiple dosing with EPIDYOLEX, the 7-OH-CBD metabolite (active in a preclinical model of seizure) circulates in human plasma at lower concentrations than the parent drug cannabidiol (~40% of CBD exposure) based on AUC.

Elimination

The plasma clearance of cannabidiol following a single 1500 mg dose of cannabidiol is about 1111 L/h. Cannabidiol is predominantly cleared by metabolism in the liver and gut and excreted in faeces, with renal clearance of parent drug being a minor pathway.

Linearity

The C_{max} and AUC of cannabidiol are close to dose-proportional over the therapeutic dose range. After single dosing, exposure over the range 750-6000 mg increases in a less than dose-proportional manner, indicating that absorption of cannabidiol may be saturable.

Pharmacokinetics in special patient groups

Effect of age, weight, sex, race

Population pharmacokinetic analyses demonstrated that there were no clinically relevant effects of age, body weight, sex, or race on exposure to cannabidiol.

Elderly patients

Pharmacokinetics of cannabidiol have not been studied in subjects > 74 years of age.

Paediatric patients

Pharmacokinetics of cannabidiol have not been studied in paediatric patients <2 years of age. A small number of patients <2 years with treatment-resistant epilepsy have been exposed to EPIDYOLEX in an expanded access programme.

Renal impairment

No effects on the C_{\max} or AUC of cannabidiol were observed following administration of a single dose of EPIDYOLEX 200 mg in subjects with mild, moderate, or severe renal impairment when compared to patients with normal renal function. Patients with end-stage renal disease were not studied.

Hepatic impairment

No effects on cannabidiol or metabolite exposures were observed following administration of a single dose of EPIDYOLEX 200 mg in subjects with mild hepatic impairment.

Subjects with moderate and severe hepatic impairment showed higher plasma concentrations of cannabidiol (approximately 2.5–5.2-fold higher AUC compared to healthy subjects with normal hepatic function). EPIDYOLEX should be used with caution in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment. The dose titration should be performed as detailed in [section 4.2](#).

Pharmacokinetic/pharmacodynamic relationship(s)

In patients with LGS, population pharmacokinetic pharmacodynamic (PK/PD) modelling indicated the presence of an exposure efficacy relationship for the likelihood of achieving a $\geq 50\%$ reduction in drop seizure frequency across the EPIDYOLEX dose range tested (0 [placebo], 10 and 20 mg/kg/day). There was a significant positive correlation between the derived AUC of cannabidiol and the probability of a $\geq 50\%$ response. The responder rate analysis also showed a correlation in the exposure-response relationship for the active metabolite of cannabidiol (7-OH-CBD). PK/PD analysis also demonstrated that systemic exposures to cannabidiol were correlated with some adverse events namely elevated ALT, AST, diarrhoea, fatigue, GGT, loss of appetite, rash, and somnolence (see [section 4.8](#)). Clobazam (separate analysis) was a significant covariate which caused the probability of GGT to increase, loss of appetite to decrease, and somnolence to increase.

Drug interaction studies

In vitro assessment of drug interactions

Cannabidiol is a substrate for CYP3A4, CYP2C19, UGT1A7, UGT1A9 and UGT2B7.

In vitro data suggest that cannabidiol is an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9 and UGT2B7-mediated activity at clinically relevant concentrations. The metabolite 7-carboxy-cannabidiol (7-COOH-CBD) is an inhibitor of UGT1A1, UGT1A4 and UGT1A6-mediated activity, *in vitro* at clinically relevant concentrations (see also [section 4.5](#)).

Cannabidiol induces CYP1A2 and CYP2B6 mRNA expression at clinically relevant concentrations.

Cannabidiol and the metabolite 7-OH-CBD do not interact with the major renal or hepatic uptake transporters and therefore are unlikely to result in relevant drug-drug interactions: OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, OATP1B1, and OATP1B3. Cannabidiol is not a substrate for or an inhibitor of the brain uptake transporters OATP1A2 and OATP2B1. *In vitro*, cannabidiol and 7-OH-CBD are not substrates for or inhibitors of efflux transports P-gp/MDR1, BCRP or BSEP. Inhibition of P-gp mediated efflux by cannabidiol in the intestine cannot be ruled out. *In vivo* data show that cannabidiol can affect P-gp-mediated efflux of a P-gp substrate in the intestine (see [section 4.5](#)). The metabolite 7-COOH-CBD is a P-gp/MDR1 substrate and has the potential to inhibit BCRP, OATP1B3, and OAT3.

In vivo assessment of drug interactions

Drug interaction studies with AEDs

Potential interactions between EPIDYOLEX (750 mg twice daily in healthy volunteers and 20 mg/kg/day in patients) and other AEDs were investigated in drug-drug interaction studies in healthy volunteers and in patients and in a population pharmacokinetic analysis of plasma drug concentrations from placebo-controlled studies in the treatment of patients with LGS.

The combination of EPIDYOLEX with clobazam caused an elevation in exposure to the active metabolite *N*-desmethylclobazam with no effect on clobazam levels. Although exposure to EPIDYOLEX was not notably affected by clobazam use, the levels of an active metabolite, 7-OH-CBD, were elevated by this combination. Therefore, dose adjustments of EPIDYOLEX or clobazam may be required. The interactions for clobazam and other concomitant AEDs are summarised in [Table 5](#).

Table 5: Drug interactions between EPIDYOLEX and concomitant antiepileptic drugs

Concomitant AED	Influence of AED on cannabidiol	Influence of cannabidiol on AED
Clobazam	No effect on cannabidiol levels. Interaction resulting in an increase in exposure of the active metabolite 7-OH-CBD in HV* studies. ^a	No effect on clobazam levels. Interaction resulting in approximately 3-fold increase in <i>N</i> -desmethylclobazam metabolite exposure. ^b
Valproate	No effect on cannabidiol or its metabolites.	No effect on valproic acid exposure or exposure to the putative hepatotoxic metabolite 2-propyl-4-pentenoic acid (4-ene-VPA).
Stiripentol	No effect on cannabidiol levels. Interaction resulting in a decrease (approximately 30%) in C _{max} and AUC of the active metabolite 7-OH-CBD in trials conducted in HV* and patients with epilepsy.	Interaction resulting in an approximately 28% increase in C _{max} and 55% increase in AUC in a HV study and increases of 17% in C _{max} and 30% increases in AUC in patients.
Everolimus	The effect of everolimus on cannabidiol has not been assessed.	Co-administration of cannabidiol (12.5 mg/kg twice daily) with everolimus (5 mg) resulting in an approximate 2.5-fold increase in everolimus exposure for both C _{max} and AUC in a HV* study.

^a average increases of 47% in AUC and 73% in C_{max}

^b based on C_{max} and AUC

* HV=Healthy Volunteer

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cannabidiol and the abundant human metabolite 7-COOH-CBD were not mutagenic in bacterial reverse mutation (Ames) assays, did not induce structural chromosomal aberrations in the *in vivo* rat micronucleus test, and did not induce DNA strand breaks in the Comet assay. The active metabolite 7-OH-CBD was not mutagenic in the bacterial reverse mutation (Ames) assay.

Carcinogenicity

In a carcinogenicity study in mice, oral administration of cannabidiol for 2 years resulted in an increased incidence of hepatocellular adenomas in male mice at 300 mg/kg/day. No significant effects were seen in females at this dose or males at the intermediate dose of 100 mg/kg/day,

corresponding to plasma exposures (AUC) approximately 12 and 5 times, respectively, the anticipated exposure in humans at the maximum recommended human dose (20 mg/kg/day).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sesame oil
Ethanol absolute
Sucralose
Strawberry flavour 501094A

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

Unopened bottle: 2 years.

Use within 8 weeks after first opening the bottle.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Amber glass bottle (type III) with a child resistant and tamper evident screw cap (polypropylene). The bottle is packaged in a carton with two 5 mL and two 1 mL calibrated oral dosing syringes (plunger HDPE and barrel polypropylene) and two bottle adapters (LDPE).

The 5 mL syringes are graduated in 0.1 mL increments and the 1 mL syringes are graduated in 0.05 mL increments.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Chiesi New Zealand Limited
Suite 1, 470 Parnell Road,
Parnell
Auckland 1052
Telephone: 09 951 3003
Email: medicalaffairs.au@chiesi.com

9. DATE OF FIRST APPROVAL

19 January 2023

10. DATE OF REVISION OF THE TEXT

05 October 2023

Summary table of changes

Section changed	Summary of new information
4.2	Updates to the administration advice with respect to food and dosing information for elderly patients.
4.4	Addition of the precaution for sesame oil.
4.5	Updates to drug interaction information for stiripentol, everolimus, CYP1A2 substrates and P-gp substrates.
4.8	Addition of expanded information relating to pneumonia.
4.9	Clarification of the severity of diarrhoea and somnolence events.
5.1	Updates to the open-label extension data.
5.2	Updates to information regarding food, alcohol and drug interaction information.
5.3	Updates to genotoxicity and carcinogenicity information.
All	Minor editorial and formatting changes.