Date: 12 April 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Epidyolex

International non-proprietary name: cannabidiol
Pharmaceutical form: solution
Dosage strength: 100 mg
Route(s) of administration: oral
Marketing Authorisation Holder: DRAC AG
Marketing Authorisation No.: 67590
Decision and Decision date: approved on 10 February 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCS	Biopharmaceutics Classification System
BID	Twice a day
cAEDs	Concomitant antiepileptic drugs
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DS	Dravet syndrome
EEG	Electroencephalogram
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
ILAE	International League Against Epilepsy
INN	International Nonproprietary Name
LC	Liquid chromatography
LGS	Lennox-Gastaut syndrome
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRI	Magnetic resonance imaging
MS	Mass spectrometry
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
QTc	QT interval corrected for heart rate
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment Emergent Adverse Event
Tmax	Time of maximum concentration observed
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
ULN	Upper limit of normal range

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance cannabidiol of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 18 July 2019.

2.2 Indication and Dosage

2.2.1 Requested Indication

Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.

2.2.2 Approved Indication

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

2.2.3 Requested Dosage

The recommended starting dose of cannabidiol 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 full monitoring schedule.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	11 June 2019
Formal control completed	10 July 2019
List of Questions (LoQ)	7 November 2019
Answers to LoQ	4 February 2020
Predecision	1 May 2020
Answers to Predecision	30 June 2020
Second Predecision	28 September 2020
Answers to second Predecision	12 November 2020
Final Decision	10 February 2021
Decision	approval

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3 Medical Context

Lennox–Gastaut Syndrome (LGS)

LGS is a rare epileptic encephalopathy that accounts for around 2-5% of childhood epilepsy. The incidence is between 0.1-0.3 per 100,000, and boys are more often affected. The onset of LGS usually occurs between 1 and 7 years of age and is characterised by the presence of multiple seizure types (predominantly tonic, atonic, and atypical absence seizures). In addition, atonic seizures with resulting falls ("drop attacks") occur in over half of the patients. Non-convulsive status epilepticus occurs in about 50% of patients with LGS. In the majority of patients, cognitive impairments occur over time, and psychomotor skills are often reduced. Behavioural problems, with progression to psychosis, are also possible.
The causes of LGS vary. Although no cause is identified in 25% of cases (idiopathic/cryptogenic LGS), de novo mutations in different genes (SCN1A, SLC2A1, STXBP1, DNM1, GABRB3) that could play an aetiological role have been found. In the remaining 75% of cases, there is mostly diffuse cerebral damage (secondary/symptomatic LGS): The causes of such damage can be tuberous sclerosis and other cerebral developmental disorders, including meningoencephalitis, traumatic cerebral damage or metabolic causes. There is a history of West syndrome in around 30% of children with LGS. The secondary form of LGS usually has a worse prognosis than the idiopathic form.
LGS is diagnosed clinically and by means of an electroencephalogram (EEG); the EEG typically shows a general slowdown with intermittent spike-wave complexes and rapid paroxysms. Treatment depends on the type of seizure, and an anti-epileptic drug may reduce one type of seizure and increase the other type. Valproate, lamotrigine, and topiramate are used as first-line drugs. Many other antiepileptic drugs are used, but most are not authorised for this indication. In Switzerland, clonazepam as monotherapy, felbamate as adjunctive therapy, rufinamide as adjunctive therapy, topiramate as adjunctive therapy and valproate as monotherapy are approved for LGS. A ketogenic diet can help reduce seizure frequency. Vagus nerve stimulation appears to be effective in drop attacks and tonic-clonic seizures.
The prognosis for LGS is generally poor, with mortality between 3% and 7% within the first 10 years after manifestation. The prognosis for idiopathic LGS seems to be slightly better, but the outcome in terms of seizure control and cognitive abilities is worse if there is a history of West syndrome.

Dravet Syndrome (DS)

Dravet syndrome (DS) is one of the most severe forms of epilepsy in early childhood and is often resistant to therapy. Dravet syndrome is also referred to as "severe myoclonic epilepsy of infancy" (SMEI). The incidence is estimated to be 1: 22,000-40,000 based on studies in the UK and Denmark. The first attack typically occurs in the first year of life (3rd to 9th month of life). In the course of the disease, there is often delayed psychomotor development, and neurological symptoms (ataxia, pyramidal signs and interictal myoclonus, more rarely cognitive deficits) develop from the age of two. The seizures are often prolonged (> 20 minutes), frequently result in status epilepticus (convulsive and non-convulsive) in infants and young children, and are often associated with fever.
In principle, different types of epileptic seizures (focal, generalised, secondary-generalised, non-convulsive) can occur. The diagnosis is made clinically, the EEG is usually inconclusive at the beginning of the manifestation and often unremarkable. As the condition progresses, spike-wave complexes can occur. The cerebral MRI is usually normal.
In 2001, a mutation associated with DS was discovered - a genetic defect (point mutation or complete absence) of the SCN1A gene was found in up to 80% of cases. The mutation of the SCN1A gene leads to a dysfunction of the NaV1.1 channel, which mainly affects GABAergic neurons. The resulting inhibition of the GABAergic inhibitory interneurons leads to excessive excitation. This explains the symptoms of the disease: epilepsy (cortical interneurons), ataxia (cerebellum), stooped gait posture with Parkinsonian gait (basal ganglia, motor neurons), thermal dysregulation and sleep disorders (hypothalamus), delayed psychomotor development (all structures mentioned above). From the age of 2 years on, psychomotor development is delayed. Mental retardation can be caused by the SCN1A gene mutation itself or by the accumulated prolonged seizures. In addition, but less frequently,

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genetic changes in other genes (PCDH19, GABRG2, SCN1B and SCN2A) can also be identified in patients with a DS/DS-like phenotype.
In pharmacotherapeutic terms, valproate is usually administered initially, in combination with clobazam in the case of resistance to therapy. According to the current therapy guidelines (ILAE, 2015), stiripentol/diacomit is mainly indicated in combination therapy with valproate and/or clobazam. This combination has been considered the gold standard since stiripentol was approved by the EMA. In addition to drug therapy, a ketogenic diet can improve seizures. Sodium channel blockers (such as lamotrigine, carbamazepine, phenytoin) worsen the disease.
The prognosis of DS with regard to freedom from seizures is also unfavourable with the use of medication (even if the frequency of seizures tends to decrease in adulthood) and with regard to cognitive development. The mortality rate is around 16%, associated with, for example, sudden unexpected death in epilepsy (SUDEP) or other causes.

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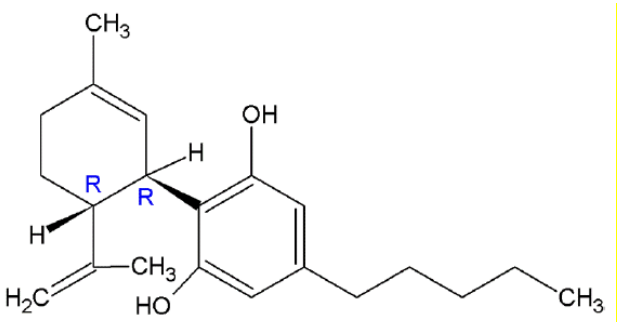
4 Quality Aspects

4.1 Drug Substance

INN: Cannabidiol
Chemical name: 2-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol
Molecular formula: $C_{21}H_{30}O_2$
Molecular mass: 314.5 g/mol
Molecular structure:



Cannabidiol is a white to yellow powder. It is lipophilic and practically insoluble in aqueous media irrespective of pH.
Cannabidiol is a highly purified crystalline substance extracted from the Cannabis sativa L. plant.
The drug substance specification includes relevant tests for proper quality control, encompassing e.g. tests relating to identification, assay, and impurities.
Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug Product

Epidyolex is an oral solution. The solution is clear and colourless to yellow. Cannabidiol is dissolved in sesame oil, ethanol with sweetener and flavouring agent. The cannabidiol concentration is 100 mg/mL.
The composition of the product is adequately described, qualitatively and quantitatively.
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data, and including batch manufacturing formula and in-process controls.
Adequate validation data pertaining to the commercial manufacturing process are available.
The drug product specification covers relevant physicochemical characteristics, as well as identification, assay and purity tests. They allow for proper control of the drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the finished product.
The finished product is packaged in an amber glass bottle with a tamper-evident child-resistant screw cap. Each package contains two bottle adapters and two 1 mL and two 5 mL oral dosing syringes.
Appropriate stability data have been generated for the drug product in the packaging material intended for marketing and following the relevant international guidelines. The data show good stability of the finished drug product and allow for a distinct assignment of the shelf life.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Epidyolex, Swissmedic conducted an abridged evaluation, which was based on the following documents: the FDA Pharmacology Review (NDA 210365) dated 14 June 2018; the EMEA/H/C/004675 Day 180 Information Request of 15 November 2018 and the 2nd List of Outstanding Issues of 31 January 2019; the EMA Assessment Report (EMEA/H/C/004675/0000) dated 25 July 2019.
The major human metabolite (7-COOH-CBD) was not adequately assessed in the nonclinical studies. Swissmedic agrees with the conclusion of the foreign agencies that this is a significant deficiency. However, the nonclinical studies to characterise the toxicity of 7-COOH-CBD can be conducted post-marketing as the product is approved based on adequate clinical data for this serious unmet medical need.
These studies with the metabolite include an embryofoetal development study, a pre- and postnatal development study, a juvenile animal toxicology study, and a carcinogenicity study in rats, as well as genotoxicity studies.
There were no particular safety issues identified in the nonclinical studies with the drug substance that would be of concern for human use. The safety margins regarding cannabidiol are considered sufficient. The nonclinical data relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME

Absorption
CBD was classified as BCS II/IV substance (low solubility, moderate permeability). The proposed commercial formulation is an oral solution, which was administered in the majority of the clinical studies.

The administration of CBD with a high–fat, high-calorie meal was associated with a 4.9-fold increase in the CBD Cmax and a 4-fold increase in the CBD AUC. Therefore, consistency with regard to food is required for CBD administration on an individual patient base.

CBD Tmax was about 4 to 5 h and not significantly changed by food intake.

The absolute bioavailability of CBD was 6.5%.

Dose Proportionality
After fasted administration of single doses between 1500 mg and 6000 mg CBD or multiple doses between 750 mg and 1500 mg BID, there was a less than dose proportional increase in the exposure of CBD and its metabolites 6-OH-CBD, 7-OH-CBD and 7-COOH-CBD.

Pharmacokinetics after multiple Dosing
After twice daily dosing, CBD and its metabolites reached steady state after 2 to 5 days. There was a 2- to 3- fold accumulation of CBD, 6-OH-CBD and 7-OH-CBD. The metabolite 7-COOH-CBD showed a 4.5- to 9.6-fold accumulation.

Distribution
The plasma protein binding of CBD and its metabolites was high (≥ 94%) and independent of concentration. The CBD volume of distribution after intravenous administration was approximately 880 L.

Metabolism
CBD was mainly metabolised by CYP3A4 and CYP2C19 in vitro. Furthermore, UGT1A7, 1A9 and 2B7 were involved in its in vitro metabolism.

No clinical mass balance study with administration of a ^{14}C-labelled CBD dose was conducted. The plasma concentrations of the following metabolites were measured by validated LC-MS/MS assays:

- 7-COOH-CBD is not pharmacologically active and reached the highest plasma concentrations of all measured analytes (30- to 50- fold higher than CBD)
- 7-OH-CBD is pharmacologically active and reached similar, or slightly lower, plasma concentrations than CBD.
- 6-OH-CBD is not pharmacologically active and showed only low plasma concentrations (< 10% of CBD).

In patients with epilepsy, the mean metabolite/parent ratios after therapeutic dosing were 0.03, 51.5 and 0.4 for 6-OH-CBD, 7-COOH-CBD and 7-OH-CBD, respectively. The metabolite/parent ratios were considerably lower after intravenous compared to oral administration, indicating a high first-pass metabolism.

Elimination
The half-life of CBD and its metabolites was about 56 h to 61 h.

Special Populations

The CBD exposure increased with decreasing hepatic function. Increases of 1.57-, 2.39- and 2.57-fold in CBD Cmax and of 1.48-, 2.45- and 5.15-fold in CBD AUC were observed in subjects with mild,

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moderate and severe hepatic impairment, respectively. The metabolite concentrations also showed an increase with decreasing hepatic function. However, the differences between subjects with moderate or severe hepatic impairment were small.

Mild, moderate or severe renal impairment had no effect on CBD or 7-COOH exposure. For 6-OH-CBD and 7-OH-CBD, there was a trend of increasing exposure (up to 2-fold for 6-OH-CBD, up to 1.56-fold for 7-OH-CBD) with decreasing renal function.

The pharmacokinetic data support the proposed dosing recommendations in these patient populations.

The pharmacokinetics of CBD and its metabolites in children and adolescents was evaluated in several population pharmacokinetic analyses. No effect of body weight or age on the pharmacokinetics of CBD and its metabolites was detected, which is quite unusual in a paediatric population. However, there were several technical flaws and inconsistencies in the analyses, casting some doubts on their validity. This means, there are no reliable pharmacokinetic data available for a large part of the target patient population.

Interactions

In vitro Data

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

The inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9 and UGT2B7 at therapeutic exposure cannot be excluded. In addition, 7-COOH-CBD is likely to inhibit UGT1A1, UGT1A4 and UGT1A6 at clinically relevant exposures.

CBD also induces CYP1A2 and 2B6 at clinically relevant exposures.

The *in vitro* interactions with transporters are summarised below:

Transporter	**CBD**	**7-OH-CBD**	**7-COOH-CBD**
Pgp	S: No I: Yes (intestinal)	S. No I: No	S. Yes
BCRP	S: No I: Yes (intestinal)	S. No I: No	I: Yes
OATP1B1	S: No I: Yes	S. No I: No	I: Yes
OATP1B3	S: No I: Yes	S: No I: No	I: Yes
OATP1A2	S: No		
OATP2B1	S: No		
OAT1	I: potentially after fed administration	I: No	I: No
OAT3	I: potentially after fed administration	I: No	I: Yes
OCT1	I: potentially after fed administration	I: No	I: No
OCT2	I: potentially after fed administration	I: No	I: No
MATE1	I: potentially after fed administration	I: No	I: No
MATE2K	I: potentially after fed administration	I: No	I: No
BSEP	I: No	I: No	I: No

S=substrate, I=inhibitor

Clinical Data

Neither itraconazole (strong CYP3A4 and Pgp inhibitor) nor fluconazole (strong CYP2C19 inhibitor) had a major impact on the exposure of CBD and its metabolites.

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Rifampicin (strong inducer of CYPs, also induces transporters after multiple dosing) also had a small impact only on CBD exposure (Cmax 34% ↓, AUC 31.5% ↓), but it reduced the exposure of the active metabolite 7-OH-CBD (Cmax 66.7% ↓, AUC 62.5% ↓). The 7-COOH-CBD Cmax was not affected by the co-administration of rifampicin, but there was a 47.8% reduction in its AUC.

The commonly co-administered AEDs stiripentol and valproate had no effect on the exposure of CBD or its metabolites. The co-administration of clobazam resulted in a 1.73-fold increase in 7-OH-CBD Cmax. Its effect on CBD and 7-COOH-CBD exposure was lower.

Co-administration of CBD had no effect on midazolam exposure, but it caused a doubling of the 1-OH-midazolam AUC. This effect was most likely due to the inhibition of UGT2B7 and/or UGT1A4 by CBD and its metabolites.

The co-administration of CBD had no effect on the exposure of clobazam in healthy subjects or epilepsy patients, but it caused a 2.6- to 4.3-fold AUC increase in the active metabolite N-CLB.

The co-administration of CBD had no effect on the exposure of valproate, its metabolite 4-ene-VPA or stiripentol.

Pharmacodynamics

CBD caused no QTc prolongation after fasted single dose administration of 750 mg and 4500 mg. However, there was only a 1.6-fold increase in CBD exposure after the 6-fold increase in dose, i.e., the tQT study covered only the expected therapeutic exposure after fasted, but not after fed, administration. No supra-therapeutic exposure was achieved. A tQT study after fed administration is planned. The report of this study shall be submitted as a “Zulassungauflage” [authorisation condition].

The CBD abuse potential after fasted single dose administration of 750 mg, 1500 mg and 4500 mg was low compared to alprazolam and dronabinol. However, the CBD exposure after 1500 mg and 4500 mg was similar to the exposure after 750 mg. Again, the therapeutic exposure after fed administration was not covered by the study.

No formal pharmacodynamic interaction studies with other centrally acting substances were conducted.

6.2 Dose Finding and Dose Recommendation

The dose determination in study GWEP1332A is primarily based on the tolerability of different doses, and a maximum dose of 20 mg/kg/day (CBD20) was set by a Data Safety Monitoring Committee (DSMC). Explicit testing of different dosages on the basis of an efficacy endpoint was not carried out in the GWEP1332A study.

6.3 Efficacy

Adjunctive therapy in patients with Lennox-Gastaut syndrome (LGS):

The efficacy of CBD for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) was evaluated in two randomised, double-blind, placebo-controlled, parallel-group studies (GWPCARE3 = study 1414 and GWPCARE4 = study 1423). 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 15 years and 94% were taking 2 or more concomitant AEDs (cAEDs) during the trial. The most commonly used cAEDs (> 25% of patients) in both trials were valproate, clobazam, lamotrigine, levetiracetam, and rufinamide. Patients received doses of CBD 10 mg/kg/day (CBD10) CBD 20 mg/kg/day (CBD20) or placebo in addition to concomitant AEDs in GWEPCARE3, and CBD 20 mg/kg/day or placebo in GWEPCARE4.

The primary endpoint was the percentage change from baseline in drop seizures per 28 days over the treatment period for the CBD group compared to placebo. Drop seizures were defined as atonic, tonic, or tonic-clonic seizures. 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 (S/CGIC) at the last visit.

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Efficacy results:
After the maintenance treatment period of 12 weeks in study GWPCARE3, the frequency of drop seizures was reduced by a median of 37% with CBD10, 42% with CBD20 and 17% with placebo; the differences to placebo were significant in each case. In the CBD10 treatment group, a 50% reduction in drop seizures was achieved in 35.6% and, in the CBD20 treatment group, in 39.5% of cases (secondary endpoint; placebo 14.5%, treatment groups each statistically significantly better than placebo; CBD10 OR3.3, p = 0.003; CBD20 OR3.9, p = 0.0006). The general frequency of seizures was reduced by a median of 36% under CBD10, by 38% under CBD20 and by 18% under placebo; the differences to placebo were significant in each case. When looking at "non-drop" seizures only, the GWPCARE3 study documented a significant, but less robust, effect on seizure frequency (placebo -34%; CBD10 -61%, p = 0.0028; CBD20 -55%, p = 0.0255). A clear deterioration in the "Global Impression of Change" - GIC ("much worse") across all verum groups was well below 5%. There was a clear surplus of patients in the verum groups who were assessed as (very) much improved.
After the maintenance treatment period of 12 weeks in study GWPCARE4, the frequency of drop seizures was reduced by 44% with CBD20 and by 22% with placebo; the differences from placebo were significant. In the CBD20 treatment group, a 50% reduction in drop seizures was achieved in 44.2% of the patients versus 23.5% of patients in the placebo group (OR 2.57, p = 0.0043). Overall, fewer seizures occurred with CBD20 (CBD20: -41 per 28 days vs. placebo -14). When looking at non-drop seizures only, the GWPCARE4 study documented a significant effect on seizure frequency (placebo -23%; CBD20 -49%, p = 0.0044).

Adjunctive Therapy in Patients with Dravet Syndrome
The efficacy of CBD for the adjunctive therapy of seizures associated with Dravet syndrome (DS) was evaluated in two randomised, double-blind, placebo-controlled, parallel-group studies (GWPCARE2 = = study 1424 and GWPCARE1 = study 1332). 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. Patients received doses of CBD 10 mg/kg/day, CBD 20 mg/kg/day or placebo in addition to concomitant AEDs in GWEPCARE2, and CBD 20 mg/kg/day or placebo in GWEPCARE1.
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 median percentage change in convulsive seizures per 28 days over the treatment period for the CBD group compared to placebo (GWPCARE1). Convulsive seizures were defined as all countable 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.

Efficacy results:
After the maintenance treatment period of 12 weeks in study GWPCARE2, the incidence of convulsive seizures was reduced by a median of 48.7% for CBD10, 45.7% for CBD20 and 26.9% for placebo; the differences from placebo were significant in each case. The general frequency of seizures was reduced by a median of 56.4% with CBD10, by 47.3% with CBD20 and by 29.7% with placebo; the differences from placebo were significant in each case. The response rate (≥ 50% seizure reduction) for convulsive seizures in the GWPCARE2 study was 49.2% for the CBD20 group, 43.9% for the CBD10 group and 26.2% for the placebo group. The effectiveness of CBD in non-convulsive seizures could not be statistically shown in the higher dosage (CBD20). A reduction of 54.7% in the CBD20 group was shown (66.2% in the CBD10 group), but a marked reduction in non-convulsive seizures of 42.9% was also demonstrated in the placebo group.

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After the maintenance treatment period of 12 weeks in study GWPCARE1, the incidence of convulsive seizures was reduced by a median of 38.9% with CBD20 and by 13.3% with placebo; the difference to placebo was significant (p = 0.012). The responder rate (≥ 50% seizure reduction) for convulsive seizures was 42.6% in the CBD20 group and 27.1% in the placebo group, the difference was not statistically significant (p = 0.078). In a post-hoc subgroup analysis, a statistically significant difference was found for the verum group in which clobazam was also taken compared to the placebo group with clobazam (responder rate placebo 23.7%, n = 38 vs. CBD20 47.5%, n = 40, p = 0.035). The total seizure frequency was reduced by a median of 28.6% with CBD20 and by 9% with placebo; the difference to placebo was significant (p = 0.033).

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, in patients with LGS treated for 37 to 48 weeks (n = 299), the median percentage reduction from baseline in drop seizure frequency was 55% during Weeks 1–12, which was maintained through to Weeks 37–48 (60%).
Across both randomised DS studies, 97.7% of patients who completed the studies were enrolled into GWPCARE5. In this study, in patients with DS treated for 37 to 48 weeks (n = 214), the mean percentage reduction from baseline in convulsive seizure frequency was 56% during Weeks 1–12, which was maintained through to Weeks 37–48 (54%).

For further details, please see the “Properties/effects” and “Clinical efficacy” sections of the information for healthcare professionals.

6.4 Safety

Exposure

In the four placebo-controlled studies, 456 patients were exposed to CBD (221 patients with DS, and 235 patients with LGS). In the open-label long-term study, an additional 644 patients were exposed to CBD (278 patients with DS, and 366 patients with LGS). Based on these five trials, 253 patient years of exposure in patients with DS and 385 patient years of exposure in patients with LGS were documented. Since DS and LGS are orphan diseases, the safety data are considered limited, but sufficient.

Adverse Events

The most common TEAEs in both pool DS and pool LGS were somnolence, decreased appetite, and diarrhoea. In pool DS, the incidences of these TEAEs were as follows: somnolence (26.7% of patients in the all-CBD group vs. 12.2% in the placebo group), decreased appetite (24.0% vs. 10.7%), diarrhoea (21.7% vs. 11.5%). In pool LGS, the incidences of these TEAEs were lower than pool DS: somnolence (22.1% in the all-CBD group vs. 7.5% in placebo group), decreased appetite (18.3% vs. 5.0%), and diarrhoea (14.9% vs. 8.1%).

In the controlled safety database, discontinuations due to adverse events were reported in 2.7% of patients taking CBD10, 11.8% of patients taking CBD20 and 1.3% in patients on placebo. Adverse events leading to discontinuation were most notable for transaminase elevations and somnolence.

In the open-label long-term study, most common AEs included diarrhoea (34.2%), pyrexia (28.4%), somnolence (25.9%), decreased appetite (23.6%), convulsion (23.0%), vomiting (19.9%), upper respiratory tract infection (18.2%), nasopharyngitis (16.0%), cough (10.6%), and status epilepticus (10.2%).

Serious Adverse Events

The most common serious TEAEs in the all-CBD group were status epilepticus, pneumonia, convulsion, and AST increased. The most common serious TEAEs were different between the 2 pools. In pool LGS, the most common serious TEAEs in the all-CBD group were status epilepticus (5.1% in the all-CBD group vs. 2.5% in the placebo group), pneumonia (3.4% vs. 0%), and AST

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increased (2.6% vs. 0%). In pool DS, the 3 most common serious TEAEs in the all-CBD group were status epilepticus (7.2% in the all-CBD group vs. 8.4% in the placebo group), convulsion (2.7% vs. 2.3%), and pneumonia (2.7% vs. 0%).

Deaths

One death was reported in the controlled studies, and six deaths were reported in the open-label extension study. Causes of deaths were sudden death in epilepsy (n=2), bowel obstruction with necrotic bowel and septic shock (n=1), seizure disorder with cerebral oedema and pulmonary oedema (n=1), and respiratory distress and aspiration pneumonia (n=3). Patients included in the studies were very ill with multiple diseases, and none of these deaths was regarded as treatment-related.

Safety topics of special interest

Liver dysfunction

In the controlled studies, liver dysfunction occurred significantly more frequently in the treatment group CBD20 (17.6%) than in the treatment group CBD10 (9.4%) and the placebo group (3.1%). Liver dysfunction often occurred within the first 6 weeks of treatment (79.4%). Less than 1% of Epidyolex-treated patients had ALT or AST levels greater than 20 times the ULN. There were also cases of transaminase elevations associated with hospitalisation in patients taking CBD and one case of acute hepatic failure (patient was reported to have recovered from this event after discontinuation of CBD). Risk factors for liver dysfunctions were concomitant administration of valproate and clobazam, higher dose of CBD and baseline transaminase elevations.

Somnolence and fatigue

In the CBD treatment groups, there was an increased incidence of AEs that had an influence on consciousness (somnolence) and the degree of wakefulness, with such AEs occurring more frequently under the higher dose CBD20. The most relevant quantitatively was somnolence, which occurred in 24.3% (n = 111/456) of all CBD doses (placebo 9.6%), but was rated as serious in only 1.5%. These AEs were also more frequent in patients on concomitant clobazam treatment.

Pneumonia

In the randomised studies, pneumonia occurred in a total of 4.8% under CBD10 and CBD20 compared to 0.7% in the placebo groups.

Safety conclusion

The most commonly observed adverse events in controlled clinical trials that occurred with a greater incidence in CBD-treated patients compared to placebo-treated patients were somnolence and sedation, decreased appetite and diarrhoea, transaminase elevations, and infections (pneumonia). Most events were mild to moderate in severity. Serious or severe adverse events were mostly related to transaminase elevations, somnolence, and infections. Discontinuations were greater in CBD treated patients, with most of the discontinuations related to transaminase elevations or somnolence. Some events of transaminase elevation were serious or severe. There were 7 deaths in the development programme (and an additional 12 deaths in the expanded access programme). Patients were generally ill with multiple comorbidities, and none of the deaths was considered related to CBD. The risks associated with CBD are considered as acceptable and can be managed with adequate labelling, especially regarding monitoring of liver function.

For further details, please see the “Undesirable effects” and the “Warnings and precautions” sections of the information for healthcare professionals.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

LGS and DS are rare epileptic syndromes with onset in early childhood. Both diseases are characterised by multiple seizure types that are generally refractory to many of the drugs typically used for the treatment of seizures. Both syndromes are associated with higher rates of mortality than

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in the general epilepsy population, primarily due to status epilepticus and sudden unexpected death in epilepsy patients.

Beneficial Effects

The primary endpoint was met in all four studies with an approximately 40-50% median seizure reduction (drop seizures in LGS, convulsive seizures in DS) in the active groups as compared to approximately 15-25% in the placebo groups. Primary endpoint results were also supported by secondary endpoints like responder analyses (criterion: 50% reduction of seizures vs. baseline). Overall, the shown effect sizes can be regarded as clinically relevant.
From a pharmacokinetic point of view, no dose adjustments for patients with mild hepatic impairment or renal impairment of all degrees (except dialysis patients) are required. The clinical interaction potential appeared to be lower than expected based on the in vitro data. There was neither a QTc prolongation nor a significant abuse liability at the expected therapeutic exposure after fasted administration.

Uncertainties regarding the Beneficial Effects

Long-term data for CBD are still limited in duration and number of investigated patients, but are regarded as acceptable for the two orphan indications. There was some uncertainty as to whether effects shown in the pivotal studies were independent of co-administered clobazam, since plasma levels of clobazam's active metabolite n-clobazam and CBD plasma levels were higher due to a bidirectional PK interaction. Further analyses supported the view that CBD efficacy is not dependent on clobazam co-administration.
There are considerable gaps in knowledge regarding the metabolism and interaction potential of CBD. No human mass balance data are available. The available clinical interaction data were not consistent with the predictions based on the in vitro data. So far, the clinical effects have been consistently lower than the predicted effects. Additional clinical interaction data will be available in the near future.
The pharmacodynamic studies investigating the CBD abuse liability and the potential to cause QTc prolongations were conducted after fasted administration. The CBD exposure achieved in these studies did not cover the therapeutic exposure after fed administration. A tQT study after fed administration is planned.

Unfavourable Effects

Somnolence and sedation, decreased appetite and diarrhoea, transaminase elevations and infections (pneumonia) occurred with higher frequency under CBD treatment compared to placebo. Serious or severe adverse events were mostly related to transaminase elevations, somnolence, and infections. Discontinuations were greater in CBD-treated patients, with most of the discontinuations related to transaminase elevations or somnolence.
Fed administration causes a considerable increase in CBD exposure, which is largely independent of the type of food. This requires consistency with regard to fasted or fed intake of CBD on an individual patient basis. No reliable pharmacokinetic data are available for children and adolescents, who represent a considerable part of the target population.

Uncertainties regarding the Unfavourable Effects

Long-term data for CBD are still limited in duration and number of investigated patients, which makes it likely that rare adverse events or adverse events occurring after longer exposure have not yet been documented in the clinical studies.
No restrictions regarding the intake of CBD with or without food were made in the clinical studies. No information on how the medication was taken in the clinical studies was collected. If the intake of CBD with regard to food largely differs in the study population from that in the "real" patient population, the study results may not be representative. The documentation of the pop PK analyses evaluating the CBD PK in children and adolescents was insufficient and impeded the evaluation of the analyses. The models employed raised many questions, which could not be satisfactorily resolved during the review

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process. The supposed lack of influence of body weight and/or age on CBD PK seems quite unusual in a paediatric patient population.

Conclusions

Treatment with CBD 10 mg/kg/day and 20 mg/kg/day led to statistically significant and clinically relevant effects in reducing seizure frequency in the difficult-to treat-populations of patients with LGS and DS. The risks associated with CBD are considered as acceptable and can be managed with adequate labelling, especially regarding monitoring of liver function.

Problematic from a clinical pharmacological point of view are the numerous gaps in knowledge, particularly regarding the pharmacokinetics of CBD in children and adolescents and the metabolism and clinical interaction potential of CBD. More data available on the latter will be available in the near future. Until then, these points can be dealt with accordingly in the information for healthcare professionals. Doubts about the validity of the population pharmacokinetic analyses, especially the covariable analyses, could not be resolved during the review process. The statements on the lack of influence of age, weight, gender and ethnicity on the CBD PK should therefore not be included in the information for healthcare professionals.

However, none of these points seems prohibitive for an approval.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Epidyolex was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Health professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable Effects" section for advice on the reporting of adverse reactions.

Epidyolex® 100 mg/ml, oral solution

Composition

Active substances
Cannabidiol

Excipients
Ethanol (anhydrous) 79 mg/ml
Alcohol content: 7.9% w/v is equivalent to 10% v/v anhydrous alcohol
Sesame oil (refined) 736 mg/ml
Benzyl alcohol 0.0003 mg/ml
Sucralose (E955)
Flavouring agent (Strawberry flavour)

Pharmaceutical form and active substance quantity per unit

Oral solution.
Each ml of solution contains 100 mg cannabidiol (Cannabidiol 100 mg/1 ml).
Clear, colourless to yellow solution.

Indications/Uses

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

Dosage/Administration

Initiation of treatment
The recommended starting dose of Epidyolex is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week.

Maintenance therapy
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 full monitoring schedule (see section “Warnings and precautions”).

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
If Epidyolex has 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 sections “Hepatocellular injury” and “Increased Seizure Frequency” under “Warnings and precautions”). A slower or faster down titration may be required, as clinically indicated, at the discretion of the treating physician.

Combination therapy
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 “Warnings and precautions” and “Interactions”).

Special dosage instructions

Patients with hepatic disorders
Epidyolex does not require dose adjustment in patients with mild hepatic impairment (Child-Pugh A).
Caution is required when using Epidyolex in patients with moderate hepatic impairment (Child-Pugh B). Initial-, maintenance-, and maximum dose must be roughly halved compared to that in patients with healthy livers. A maximum dose of more than 10 mg/kg/day is not recommended in these patients.
The use of Epidyolex in patients with severely impaired liver function (Child-Pugh C) is not recommended.
See also section “Warnings and precautions” and “Pharmacokinetics”.

Patients with renal disorders
Epidyolex can be administered to patients with mild, moderate, or severe renal impairment without dose adjustment (see section “Pharmacokinetics”). There is no experience in patients with end-stage renal disease. It is not known if Epidyolex is dialysable.

Elderly patients (65 years of age and above)
The safety and efficacy of Epidyolex in patients ≥ 65 years of age have not been established. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other concurrent therapy (see section “Hepatocellular injury” under “Warnings and precautions”).

Children and adolescents

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.

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

Mode 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 taking with food, a similar composition of food should be maintained as far as possible.

Contraindications

Hypersensitivity to the active substance, to sesame oil, or to any of the excipients listed in section "Composition".
If a patient develops hypersensitivity reactions after treatment with Epidyolex, the medicinal product should be discontinued.
Patients with transaminase elevations greater than 3 times the upper limit of normal (ULN) and bilirubin greater than 2 times the ULN (see section "Warnings and precautions").

Warnings and precautions

Hepatocellular injury
Epidyolex causes dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) (see section "Undesirable effects"). 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 clobazam should be considered if transaminase elevations occur.
Regression of transaminase elevations to baseline levels 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.

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 adverse event. 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, serum transaminases (ALT and AST), alkaline phosphatase and total bilirubin levels must be obtained.
Serum transaminases (ALT and AST), alkaline phosphatase and total bilirubin levels should be 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, serum transaminases and total bilirubin should be promptly measured 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. Dose adjustment of any co-administered medicinal product that is known to affect the liver should be considered (e.g., valproate and clobazam) (see section “Interactions”).

<u>Patients with moderate and severe impairment of the liver function (Child-Pugh B and C)</u>
Patients with impaired liver function were not studied in the pivotal clinical trials.
Epidyolex should be used in patients with moderate impairment of the liver function (Child-Pugh B) only after careful consideration of the benefit-risk ratio and under strict monitoring of the liver function parameters and at a reduced dose (see section “Dosage/Administration”).
The use of Epidyolex in patients with severe impairment of the liver function (Child-Pugh C) is not recommended.

<u>Somnolence and sedation</u>
Epidyolex can cause somnolence and sedation, which often occur early on in treatment and may diminish with continued treatment. The occurrence was higher for those patients on concomitant clobazam (see section “Interactions” and “Undesirable effects”). Other CNS depressants, including alcohol, can potentiate the somnolence and sedation effect.

<u>Pneumonia</u>
An increased risk of pneumonia has been observed with Epidyolex use. In the controlled clinical trials of patients with LGS or DS, 6% of Epidyolex-treated patients had pneumonia, compared to 1% of patients on placebo. The frequency of pneumonia did not appear to be dose related, with 5% of patients on Epidyolex 20 mg/kg/day experiencing pneumonia, compared to 9% of patients on Epidyolex 10 mg/kg/day. The rate of pneumonia was higher in patients taking concomitant clobazam. Prescribers should monitor patients for signs and symptoms of pneumonia, including significant somnolence and sedation.

<u>Increased seizure frequency</u>

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, should the benefit-risk ratio be negative.

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 causal 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.

Ethanol in the formulation
This medicinal product contains 7.9% w/v ethanol (alcohol) (79 mg/ml ethanol equivalent to 10% v/v anhydrous ethanol), i.e., up to 553 mg ethanol per Epidyolex dose (10 mg/kg) for an adult weighing 70 kg. This is equivalent to 14 ml of beer, or 6 ml of wine per dose.
The low quantity of alcohol in this medicinal product has no noticeable effects.

Benzyl alcohol
This medicinal product contains 0.0003 mg/ml benzyl alcohol corresponding to 0.0021 mg per Epidyolex dose (Epidyolex 10 mg/kg per dose for an adult weighing 70 kg).
Benzyl alcohol may cause allergic reactions.
There is an increased risk in small children due to accumulation.
Large quantities should only be used with caution and if absolutely necessary, because of the risk of accumulation and toxicity (“metabolic acidosis”), especially for patients with impaired hepatic or renal function, for pregnant and breast-feeding patients.

Refined sesame oil
Epidyolex contains refined sesame oil which may rarely cause severe allergic reactions.

Interactions

In vitro data
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-induced activity at clinically relevant concentrations. The metabolite 7-carboxy-cannabidiol (7-COOH-CBD) is an in vitro inhibitor of UGT1A1, UGT1A4 and UGT1A6 at clinically relevant concentrations.

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

Inhibition of P-glycoprotein or BCRP-mediated efflux by cannabidiol in the intestine cannot be ruled out.

The metabolite 7-COOH-CBD is a P-gp/MDR1 substrate and has the potential to inhibit BCRP, OATP1B1, OATP1B3, and OAT3.

Cannabidiol and the metabolite 7-OH-CBD are not substrates of Pgp, BCRP, OATP1B1 or OATP1B3.

The metabolite 7-OH-CBD is no inhibitor of the major renal or hepatic uptake transporters 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.

Cannabidiol and 7-OH-CBD are not inhibitors of efflux transporter BSEP at clinically relevant plasma concentrations.

The pharmacokinetics of Epidyolex are complex and may cause interactions with the patient's concomitant AED treatments. The dose of Epidyolex and/or concomitant AED treatment should therefore be adjusted as part of regular medical monitoring 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 (750 mg twice daily in healthy volunteers and 20 mg/kg/day in patients) with epilepsy for clobazam, valproate and stiripentol.

Although no formal drug-drug interaction studies have been performed for other AEDs, phenytoin and lamotrigine are addressed based on in vitro data. Interactions and dose recommendations with AEDs and other medicines are summarised in the table below.

Table

Concomitant Medication	**Effect on Plasma Levels Geometric Mean Ratio (90% CI)**	**Notes and Recommendations**
Antiepileptic Drugs (AEDs)		
Valproate	CBD AUC_{tau}: 1.05 (0.90, 1.24) CBD C_{max}: 0.74 (0.58, 0.93) 7-OH-CBD AUC_{tau}: 1.22 (0.96, 1.55) 7-OH-CBD C_{max}: 0.97 (0.67, 1.41) Valproate AUC_{tau}: 0.83 (0.75, 0.92) to 0.99 (0.90, 1.08) Valproate C_{max}: 0.87 (0.79, 0.95) to 1.01 (0.95, 1.07) 4-ene-VPA AUC_{tau}: 0.70 (0.62, 0.80) 4-ene-VPA C_{max}: 0.77 (0.66, 0.90)	Concomitant use of Epidyolex and valproate increases the incidence of transaminase enzyme elevations (see section "Warnings and precautions"). The mechanism of this interaction remains unknown. If clinically significant increases of transaminases occur, cannabidiol and/or valproate should be simultaneously reduced or discontinued in all patients until a recovery of transaminase elevations are observed (see section "Warnings and precautions"). Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic medicinal products and cannabidiol (see section "Warnings and precautions"). Concomitant use of Epidyolex and valproate increases the incidence of diarrhoea and events of decreased appetite. The mechanism of this interaction is unknown. There are no clinically important pharmacokinetic changes in either CBD or VPA or their metabolites.

Concomitant Medication	Effect on Plasma Levels Geometric Mean Ratio (90% CI)	Notes and Recommendations
Clobazam	CBD AUC_{tau}: 1.30 (1.00, 1.70) CBD C_{max}: 1.34 (0.93, 1.95) 7-OH-CBD AUC_{tau}: 1.47 (1.26, 1.70) 7-OH-CBD C_{max}: 1.73 (1.36, 2.20) Clobazam AUC_{tau}: 1.06 (0.90, 1.24) to 1.21 (1.05, 1.39) Clobazam C_{max}: 1.00 (0.83, 1.19) to 1.20 (1.05, 1.38) N-CLB AUC_{tau}: 2.64 (1.95, 3.58) to 3.38 (2.62, 4.36) N-CLB C_{max}: 2.22 (1.42, 3.46) to 3.39 (2.61, 4.39)	Concomitant use of Epidyolex and clobazam increases the incidence of somnolence and sedation (see section "Warnings and precautions" and "Undesirable effects"). Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co-administered with Epidyolex. When Epidyolex and clobazam are co-administered there are no effects on cannabidiol or clobazam plasma levels, however bi-directional PK interactions occur affecting their active metabolites (N-desmethylclobazam and 7-hydroxy cannabidiol). Increased systemic plasma levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions. Therefore, dose adjustments of Epidyolex or clobazam may be required.
Stiripentol	CBD AUC_{tau}: 1.03 (0.94, 1.14) CBD C_{max}: 1.13 (0.96, 1.33) 7-OH-CBD AUC_{tau}: 0.72 (0.61, 0.85) 7-OH-CBD C_{max}: 0.71 (0.51, 0.99) Stiripentol AUC_{tau}: 1.30 (1.09, 1.55) to 1.55 (1.42, 1.69) Stiripentol C_{max}: 1.17 (1.03, 1.33) to 1.28 (1.08, 1.52)	When Epidyolex was combined with stiripentol administration there was a minor increase in stiripentol plasma levels. The clinical relevance of this is unknown, but the patient should be closely monitored for adverse drug reactions. There is no effect on cannabidiol plasma levels. The interaction resulted in a decrease in C_{max} and AUC of the active metabolite, 7-OH-CBD, in healthy volunteer trials.
Phenytoin	A potential drug-drug interaction has not been studied.	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*. 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	A potential drug-drug interaction has not been studied.	Lamotrigine is a substrate for UGT enzymes including UGT2B7, which is inhibited by cannabidiol *in vitro*. Lamotrigine plasma levels may be elevated when it is co-administered with Epidyolex.
CYP2C19 Substrates / Inhibitors		
Fluconazole	CBD AUC_t: 1.21 (1.08, 1.36) CBD C_{max}: 1.24 (1.05, 1.47) 7-OH-CBD AUC_t: 0.71 (0.61, 0.82) 7-OH-CBD C_{max}: 0.59 (0.48, 0.72) The effect on fluconazole has not been studied.	Fluconazole, a potent CYP2C19 inhibitor, has only a minor effect on CBD exposure and causes a small decrease in 7-OH-CBD exposure. None of these changes are considered clinically meaningful. Epidyolex may cause increased plasma concentrations of medicines that are metabolised by CYP2C19, e.g., omeprazole and clobazam (see above). Dose reduction should be considered for concomitant medicinal products that are sensitive CYP2C19 substrates, or that have a narrow therapeutic index.

Concomitant Medication	Effect on Plasma Levels Geometric Mean Ratio (90% CI)	Notes and Recommendations
CYP2C19 Inducers		
Rifampicin	CBD AUC_t: 0.68 (0.61, 0.75) CBD C_{max}: 0.66 (0.56, 0.78) 7-OH-CBD AUC_t: 0.37 (0.33, 0.41) 7-OH-CBD C_{max}: 0.33 (0.29, 0.38) The effect on rifampicin has not been studied.	Rifampicin and other strong inducers of CYP2C19 may decrease the plasma concentration of cannabidiol and therefore decrease the effectiveness of Epidyolex.
CYP3A4 Substrates / Inhibitors		
Midazolam	Midazolam AUC_t: 0.92 (0.78, 1.09) Midazolam C_{max}: 0.80 (0.67, 0.96) 1'-hydroxymidazolam AUC_t: 1.68 (1.41, 2.01) 1'-hydroxymidazolam C_{max}: 1.12 (0.93, 1.34) The effect on cannabidiol has not been studied.	Epidyolex has no effect on the clearance of midazolam and is not expected to affect clearance of other sensitive CYP3A4 substrates.
Itraconazole	CBD AUC_t: 1.05 (0.96, 1.15) CBD C_{max}: 1.01 (0.82, 1.25) 7-OH-CBD AUC_t: 1.17 (1.07, 1.27) 7-OH-CBD C_{max}: 1.06 (0.90, 1.25) The effect on itraconazole has not been studied.	Itraconazole, a potent CYP3A4 inhibitor, does not affect CBD exposure and causes a very small, clinically insignificant increase in 7-OH-CBD exposure.
CYP3A4 Inducers		
e.g., rifampicin, carbamazepine, enzalutamide, mitotane, St. John's wort	See rifampicin study data (CYP2C19 Inducers)	Strong inducers of CYP3A4 may decrease the plasma concentration of cannabidiol and therefore decrease the effectiveness of Epidyolex. Dose adjustment may be necessary.
CYP2C8 and CYP2C9 Substrates / Inhibitors		
e.g., repaglinide, warfarin	A potential drug-drug interaction has not been studied.	Dose reduction of substrates of CYP2C8 and CYP2C9 should be considered, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with Epidyolex.
CYP1A2 and CYP2B6 Substrates / Inhibitors		
e.g., theophylline, caffeine, bupropion, efavirenz	A potential drug-drug interaction has not been studied.	Dose adjustment of substrates of CYP1A2 and CYP2B6 should be considered, as clinically appropriate.
UGT1A7, UGT1A9, and UGT2B7 Substrates / Inhibitors		
e.g., diflunisal, propofol, fenofibrate, gemfibrozil, morphine, lorazepam	A potential drug-drug interaction has not been studied.	Dose reduction of substrates of UGT1A7, UGT1A9, and UGT2B7 or of Epidyolex should be considered, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with Epidyolex.

Concomitant Medication	Effect on Plasma Levels Geometric Mean Ratio (90% CI)	Notes and Recommendations
UGT1A1, UGT1A4 and UGT1A6 Substrates / Inhibitors		
e.g., lamotrigine, olanzapine, paracetamol	A potential drug-drug interaction has not been studied.	The metabolite 7-COOH-CBD is 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.
Oral Contraceptives		
e.g., ethinylestradiol, levonorgestrel	A potential drug-drug interaction has not been studied.	Cannabidiol is not an inducer of CYP3A4 and therefore is not expected to alter the pharmacokinetics of hormonal contraceptives.

Pregnancy, lactation

Pregnancy
There are only very limited data from the use of Epidyolex in pregnant women. Studies in animals have shown reproductive toxicity (see section “Preclinical data”).
Epidyolex should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

Lactation
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 section “Preclinical data”).
Given that cannabidiol is highly protein bound and will likely pass freely from plasma into milk, breast-feeding should be discontinued during treatment.

Fertility
No data on the effects of Epidyolex on human fertility are available.
No effect on reproductive ability of male or female rats was noted with an oral dose of up to 150 mg/kg/day cannabidiol (see section “Preclinical data”).

Effects on ability to drive and use machines

Epidyolex has major influence on the ability to drive and operate machines because it may cause somnolence and sedation (see section “Warnings and precautions”). Patients should be advised not to drive or operate machinery until they have gained sufficient experience to gauge whether it adversely affects their abilities (see section “Undesirable effects”).

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 for treatment discontinuations was transaminase elevation.

Adverse reactions reported with Epidyolex in placebo-controlled clinical studies are listed below by System Organ Class and frequency.
The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

List of adverse reactions (including frequencies)

Infections and infestations
Common: Pneumonia[a], Bronchitis, Nasopharyngitis, Urinary tract infection

Metabolism and nutrition disorders
Very common: Decreased appetite (21%)
Common: Increased appetite

Psychiatric disorders
Common: Irritability, Insomnia, Aggression, Abnormal behaviour, Agitation

Nervous system disorders
Very common: Somnolence[a] (29%)
Common: Lethargy, Drooling, Tremor

Respiratory, thoracic and mediastinal disorders
Common: Cough

Gastrointestinal disorders
Very common: Diarrhoea (18%), Vomiting (11%)

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 (16%), Fatigue (11%)

Investigations
Common: Weight decreased

[a] Grouped Terms: **Pneumonia:** Pneumonia, RSV pneumonia, Mycoplasma pneumonia, Adenovirus pneumonia, , Viral pneumonia, Aspiration pneumonia; **Somnolence:** Somnolence, Sedation.

Description of specific adverse reactions

Hepatocellular injury
Epidyolex causes dose-related elevations of ALT and AST values (see section «Warnings and precautions»).
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 administration of valproate and clobazam, dose of Epidyolex and baseline transaminase elevations.

Concomitant administration of 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% of patients taking Epidyolex 10 mg/kg/day.

Baseline transaminase elevations
In controlled trials (see sections “Properties/Effects”, “Pharmacodynamics”) in patients taking Epidyolex 20 mg/kg/day, the frequency of 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. Five percent (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 it 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 the controlled trials of patients with LGS or DS, based on measured weights, 16% of Epidyolex-treated patients had a decrease in weight of ≥ 5% from their baseline weight, compared to 9% of patients on placebo. The decrease in weight appeared to be dose related, with 19% of patients on Epidyolex 20 mg/kg/day experiencing a decrease in weight ≥ 5%, compared to 8% of patients on Epidyolex 10 mg/kg/day. In some cases, the decreased weight was reported as an adverse event (see the list above). 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 controlled trials of patients with LGS or DS, the mean decrease in haemoglobin from baseline to end of treatment was −0.37 g/dL in Epidyolex-treated patients and +0.01 g/dL in patients on placebo. A corresponding decrease in haematocrit was also observed, with a mean change of −1.4% in Epidyolex-treated patients, and −0.3% in patients on placebo.
There was no effect on red blood cell indices. 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), versus 15% of patients on placebo.

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.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms
Experience with doses higher than the recommended therapeutic dose is limited. Mild to moderate 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.

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

Properties/Effects

ATC code: N03AX24

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 subtype 1 (TRPV-1) channels, as well as modulation of adenosine-mediated signalling through inhibition of adenosine intracellular uptake via the equilibrative nucleoside transporter 1 (ENT-1).

Pharmacodynamics

No specific information.

Clinical efficacy

Adjunctive therapy in patients with Lennox-Gastaut syndrome (LGS)

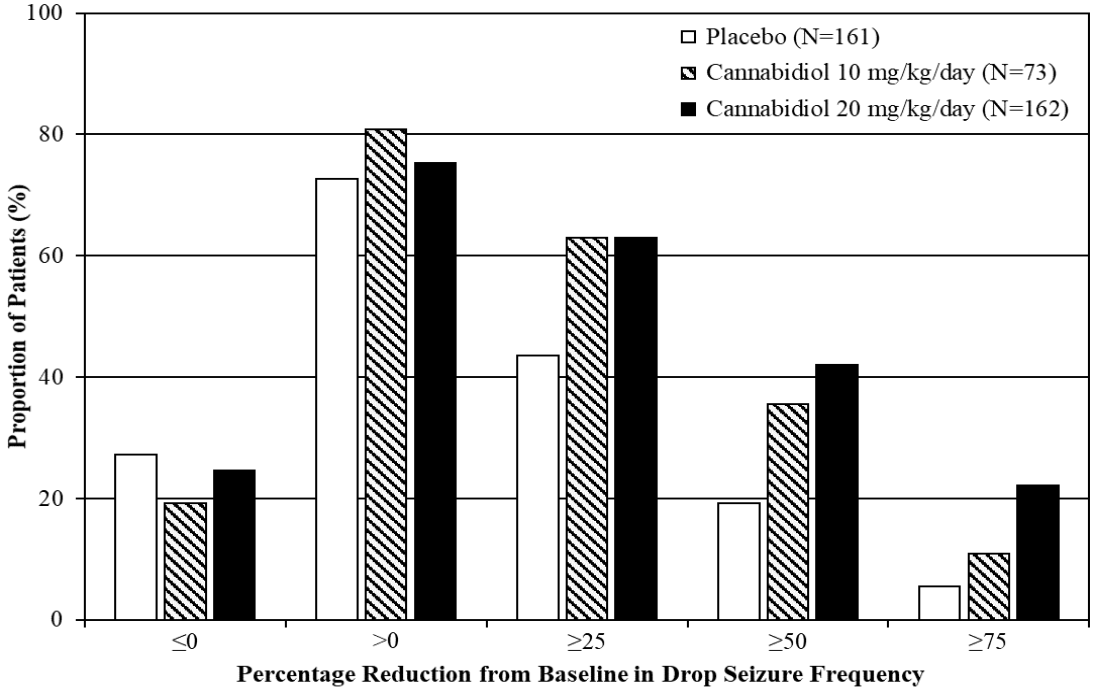
The efficacy of Epidyolex for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) was evaluated in two randomised, double-blind, placebo-controlled, parallel-group studies (GWPCARE3 and GWPCARE4). Each study consisted of a 4-week baseline period, a 2-week titration period and a 12-week maintenance period. Mean age of the study population was 15 years and 94% were taking 2 or more concomitant AEDs (cAEDs) during the trial. The most commonly used cAEDs (> 25% of patients) in both trials were valproate, clobazam, lamotrigine, levetiracetam, and rufinamide.
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. Key secondary endpoints were the proportion of patients with at least 50% reduction in drop seizure frequency, the percentage change from baseline in total seizure frequency, and Patient/Caregiver Global Impression of Change at the last visit. These outcome measures are summarized in Table 1.

Table 1: 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)
Primary endpoint *–Percentage reduction in drop seizure frequency*					
Drop seizures **Median % Reduction** ***Comparison to Placebo*** **Difference** 95% CI P-value	41.9 21.6 6.7; 34.8 0.005	37.2 19.2 7.7; 31.2 0.002	17.2	43.9 17.2 4.1; 30.3 0.014	21.8
Key secondary endpoints					
50% responder proportion[a] P-value	39.5% 0.001	35.6% 0.003	14.5%	44.2% 0.004	23.5%
Total seizures **Median % Reduction** ***Comparison to Placebo*** **Difference** 95% CI P-value	38.4 18.8 4.4; 31.8 0.009	36.4 19.5 7.5; 30.4 0.002	18.5	41.2 21.1 9.4; 33.3 0.001	13.7
Mean P/CGIC results (last visit) 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 Cannabidiol and Placebo in Patients with Lennox-Gastaut Syndrome (GWPCARE3 and GWPCARE 4)



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 3–5 days per 28 days versus placebo (20 mg/kg/day) and an additional 3 days per 28 days versus placebo (10 mg/kg/day).

Adjunctive Therapy in Patients with Dravet Syndrome

The efficacy of Epidyolex for the adjunctive therapy of seizures associated with Dravet syndrome (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.

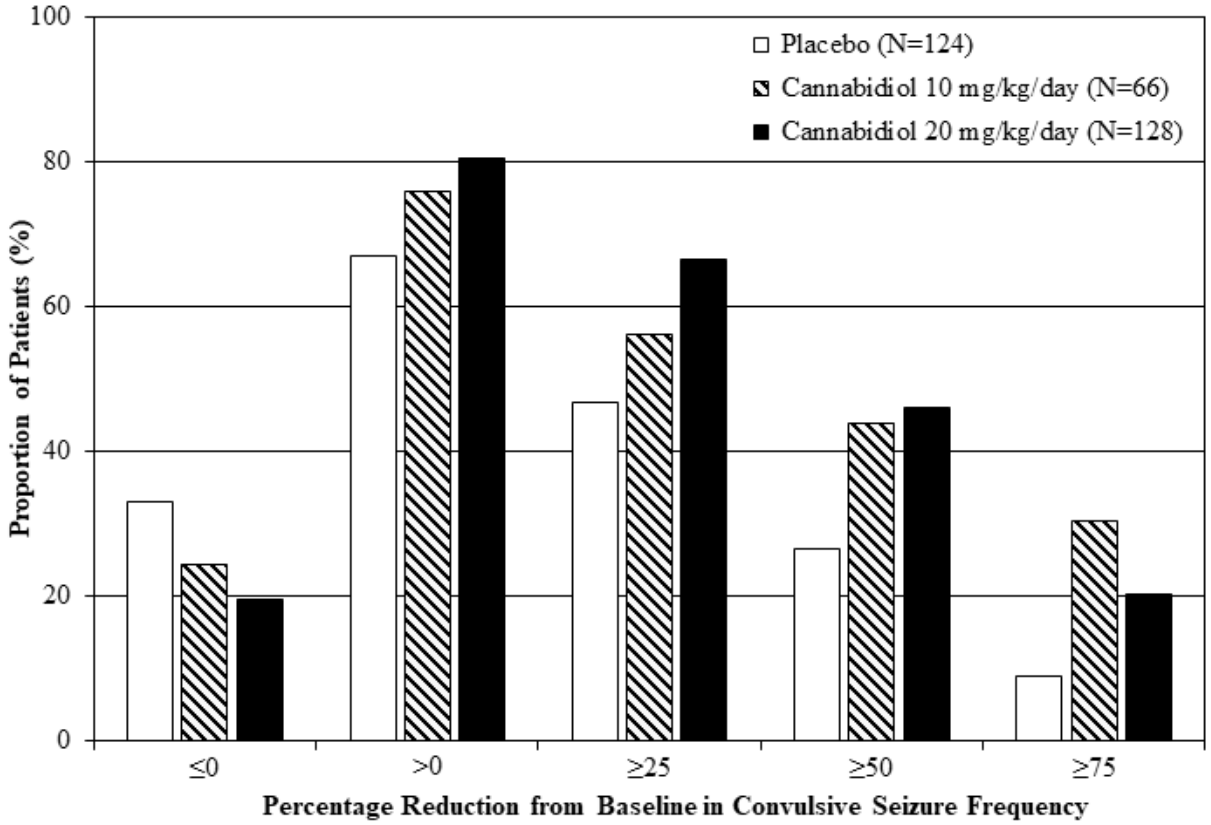
The primary endpoint was the change in convulsive seizure frequency during the treatment period (Day 1 to the end of the evaluable period) compared to baseline (GWPCARE2), and the median percentage change in convulsive seizures per 28 days over the treatment period for the Epidyolex group compared to placebo (GWPCARE1). Convulsive seizures were defined as all countable atonic, tonic, clonic, and tonic-clonic seizures. Key secondary endpoints for GWPCARE2 were the proportion of patients with at least 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 50% reduction in convulsive seizure frequency. These outcome measures are summarised in Table 2.

Table 2: 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	25.1	38.0			
Difference					
95% CI	3.5; 41.9	20.1; 51.9			
P-value	0.026	<0.001			
Mean P/CGIC results (last visit)	3.1 (sl. improved)	2.8 (sl. improved)	3.6 (no change)	*	
P-value	0.028	0.001			

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 (GWP-CARE2 and GWPCARE1)



Percentage reduction of convulsive seizure frequency

Placebo (n=124)
Cannabidiol 10 mg/kg/day (n=66)
Cannabidiol 20 mg/kg/day (n=128)
Proportion of patients (%)

Epidyolex was associated with an increase in the number of convulsive seizure-free days during the treatment period in each trial, equivalent to an additional 1 to 1.5 days per 28 days versus placebo (20 mg/kg/day) and an additional 2 to 2.5 days per 28 days versus placebo (10 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 (see Figures 1 and 2), Epidyolex should be titrated initially to the recommended maintenance dose of 10 mg/kg/day (see Section “Dosage/Administration”). In individual patients, titration up to a maximum dose of 20 mg/kg/day may be considered, based on the benefit-risk (see Section “Dosage/Administration”).

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, pneumonia and hepatocellular injury (see sections “Warnings and precautions”, “Interactions”, and “Undesirable effects”).
The concomitant use of Epidyolex and clobazam requires individualised clinical 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, in 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%).
Across both randomised DS studies, 97.7% of patients who completed the studies were enrolled into GWPCARE5. In this study, in patients with DS treated for 37 to 48 weeks (N=214), the mean percentage reduction from baseline in convulsive seizure frequency was 56% during Week 1–12, which was maintained through to Week 37–48 (54%).

Safety and efficacy in paediatric patients
The European Medicines Agency has deferred the obligation to submit the results of studies with Epidyolex in one or more subsets of the paediatric population in treatment of seizures associated with DS and LGS. See section “Dosage/Administration” for information on paediatric use.

Further information

Abuse
In an abuse potential study, acute administration of Epidyolex to non-dependent adult recreational drug users at therapeutic and supratherapeutic doses produced small responses on positive subjective measures such as “craving” and “desire to take again”. Compared to dronabinol (synthetic THC) and alprazolam, Epidyolex has low abuse potential.

Pharmacokinetics

Absorption
Cannabidiol 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 predose (C_{min}) 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.
Co-administration of Epidyolex 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.

Distribution
In vitro, > 94% of cannabidiol and its phase I metabolites were bound to plasma protein. Preferential binding is with human serum albumin.
The apparent oral volume of distribution healthy volunteers was 20,963 L to 42,849 L and greater than in total body water, suggesting a wide distribution of Epidyolex.

Metabolism

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.
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 seizure model) circulates in human plasma at lower concentrations than the parent drug cannabidiol (~ 40% of CBD exposure) based on AUC. The circulating metabolite with the highest plasma concentrations is 7-COOH-CBD with steady state exposure around 50-fold higher than CBD. This metabolite probably has no intrinsic activity.

Elimination
The half-life of Epidyolex in plasma was 56–61 hours after twice daily dosing for 7 days in healthy volunteers.
The plasma clearance of cannabidiol following a single 1500 mg dose of cannabidiol is about 1111 L/h.

Linearity/non-linearity
After single fasting dosing, cannabidiol exposure over the range 750–6000 mg increases in a less than dose-proportional manner.

Kinetics in specific patient groups

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).

Renal impairment
No effects on the Cmax 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.

Children and adolescents
Pharmacokinetics of cannabidiol has not been studied in paediatric patients < 2 years of age. A small number of patients < 2 years old with treatment-resistant epilepsy have been administered Epidyolex in an expanded access programme.

Preclinical data

Mutagenicity
Genotoxicity studies have not detected any mutagenic or clastogenic effect.

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

Reproductive toxicity
No adverse reactions were observed on male or female fertility or reproduction performance in rats at doses of up to 250 mg/kg/day.

An embryo-foetal development (EFD) study performed in rabbits evaluated doses of 50, 80, or 125 mg/kg/day. Decreased foetal body weights and increased foetal structural variations associated with maternal toxicity were observed at a dose of 125 mg/kg/day. Maternal plasma cannabidiol exposures at the no-observed-adverse-effect-level (NOAEL) 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. Embryofoetal 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 ≥ 150 mg/kg/day. The NOAEL was associated with maternal plasma cannabidiol exposures approximately 9 times that in humans at 20 mg/kg/day.

Juvenile toxicity
In juvenile rats, administration of cannabidiol for 10 weeks (subcutaneous doses of 0 or 15 mg/kg on postnatal days [PNDs] 4–6 followed by oral administration of 0, 100, 150, or 250 mg/kg on PNDs 7–77) resulted in increased body weight, delayed male sexual maturation, neurobehavioural effects, increased bone mineral density, and liver hepatocyte vacuolation. A no-effect dose was not established. The lowest dose causing developmental toxicity in juvenile rats (15 mg/kg subcutaneous / 100 mg/kg oral) was associated with Cmax cannabidiol exposures approximately 20 times that in paediatric subjects.

Other data
Non-clinical abuse potential studies showed that cannabidiol does not produce cannabinoid-like behavioural responses, including generalisation of 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.

Other information

Incompatibilities
Not applicable.

Shelf life
Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening
Shelf life after first opening: Use within 12 weeks after first opening the bottle.

Special precautions for storage
Do not store above 30°C.
Do not freeze.
Keep out of the reach of children.

Instructions for handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

67590 (Swissmedic)

Packs

Amber glass bottle (type III) with a childproof and tamperproof screw cap (polypropylene).
1 ml oral dosing syringe (graduated in 0.05 ml increments) (plunger HDPE and barrel polypropylene) and bottle adaptor (LDPE).
5 ml oral dosing syringe (graduated in 0.1 ml increments) (plunger HDPE and barrel polypropylene) and bottle adaptor (LDPE).

Each pack contains:
One 100 ml bottle
Two 1 ml oral dosing syringes with adaptor
Two 5 ml oral dosing syringes with adaptor

Dispensing category: A

Marketing authorisation holder

DRAC AG, Murten

Manufacturer

GW Pharma Limited, Sittingbourne / UK

Date of revision of the text

February 2021