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(56) Documents Cited:
WO 2019/071302 A1 **WO 2019/045121 A1**
Epilepsy & Behavior, vol. 29, 2013, Porter & Jacobson, "Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy", pages 574-577, available via https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157067/
Health Europa, 2019, "The fight for getting access to medical cannabis in the UK goes on", healtheuropa.eu, [online], available via https://www.healtheuropa.eu/access-to-medical-cannabis-in-the-uk/93025/
Dev. Med. Child Neurol., vol. 60, 2018, Kurian et al., "Focal cortical malformations in children with early infantile epilepsy and PCDH19 mutations: case report", pages 100-105, available via https://onlinelibrary.wiley.com/doi/full/10.1111/dmcn.13595
Brain and Development, vol. 40, 2018, Hausman-Kedem et al., "Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents An observational, longitudinal study", pages 544-551
N. Engl. J. Med., vol. 376, 2017, Devinsky et al., "Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome", pages 2011-2020, available via https://www.nejm.org/doi/full/10.1056/nejmoa1611618
Epilepsia, vol. 57, 2016, Hess et al., "Cannabidiol as a new treatment for drug-resistant epilepsyin tuberous sclerosis complex", pages 1617-1624, available via https://onlinelibrary.wiley.com/doi/epdf/10.1111/epi.13499
Epilepsia, vol. 60, 2019, Thiele et al., "Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study", pages 419-428, available via https://pubmed.ncbi.nlm.nih.gov/30740695/
Epilepsia, vol. 58, 2018, Rosenberg et al., "Quality of Life of Childhood Epilepsy (QOLCE) in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol (CBD)", pages 96-100, available via https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5568670/

(58) Field of Search:
Other: **WPI, EPODOC, Patent Fulltext, INTERNET, BIOSIS, MEDLINE, XPESP, NPL, XPOAC**

(54) Title of the Invention: **Use of cannabidiol in the treatment of seizures associated with rare epilepsy syndromes related to genetic abnormalities**
Abstract Title: **Use of cannabidiol in the treatment of epileptic seizures associated with PCDH19 mutation**

(57) The use of cannabidiol (CBD) for the treatment of epileptic seizures associated with rare epilepsy syndromes, the seizures treated are in patients diagnosed with a protocadherin 19 (PCDH19) mutation. In a further embodiment the types of seizures include tonic-clonic seizures. Preferably the CBD comprises greater than 98% (w/w) CBD and less than or equal to 2% (w/w) of other cannabinoids. Where the CBD is given concomitantly with one or more other anti-epileptic drugs (AED) including levetiracetam, clobazam, topiramate, gabapentin and phenytoin. Preferably the dose of CBD is between 5 mg/kg/day to 50 mg/kg/day. Preferably the CBD used is in the form of a botanically derived purified CBD, but a synthetically produced CBD can alternatively be used.

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USE OF CANNABIDIOL IN THE TREATMENT OF SEIZURES ASSOCIATED WITH RARE EPILEPSY SYNDROMES RELATED TO GENETIC ABNORMALITIES

FIELD OF THE INVENTION

[0001] The present invention relates to the use of cannabidiol (CBD) for the treatment of seizures associated with rare epilepsy syndromes. In particular the seizures associated with rare epilepsy syndromes that are treated are those which are experienced in patients diagnosed with PCDH19 Epilepsy. In a further embodiment the types of seizures include tonic-clonic seizures. Preferably the dose of CBD is between 5 mg/kg/day to 50 mg/kg/day.

[0002] In a further embodiment the CBD used is in the form of a highly purified extract of cannabis such that the CBD is present at greater than 95% of the total extract (w/w) and the cannabinoid tetrahydrocannabinol (THC) has been substantially removed, to a level of not more than 0.15% (w/w).

[0003] Preferably the CBD used is in the form of a botanically derived purified CBD which comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) of other cannabinoids. More preferably the other cannabinoids present are THC at a concentration of less than or equal to 0.1% (w/w); CBD-C1 at a concentration of less than or equal to 0.15% (w/w); CBDV at a concentration of less than or equal to 0.8% (w/w); and CBD-C4 at a concentration of less than or equal to 0.4% (w/w). The botanically derived purified CBD preferably also comprises a mixture of both trans-THC and cis-THC. Alternatively, a synthetically produced CBD is used.

[0004] Where the CBD is given concomitantly with one or more other anti-epileptic drugs (AED), the CBD may be formulated for administration separately, sequentially or simultaneously with one or more AED or the combination may be provided in a single dosage form.

BACKGROUND TO THE INVENTION

[0005] Epilepsy occurs in approximately 1% of the population worldwide, (Thurman *et al.*, 2011) of which 70% are able to adequately control their symptoms with the available existing anti-epileptic drugs (AED). However, 30% of this patient group, (Eadie *et al.*, 2012), are unable to obtain seizure freedom from the AED that are available and as such are termed as suffering from intractable or "treatment-resistant epilepsy" (TRE).

[0006] Intractable or treatment-resistant epilepsy was defined in 2009 by the International League Against Epilepsy (ILAE) as "*failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom*" (Kwan *et al.*, 2009).

[0007] Individuals who develop epilepsy during the first few years of life are often difficult to treat and as such are often termed treatment resistant. Children who undergo frequent seizures in childhood are often left with neurological damage which can cause cognitive, behavioral and motor delays.

[0008] Childhood epilepsy is a relatively common neurological disorder in children and young adults with a prevalence of approximately 700 per 100,000. This is twice the number of epileptic adults per population.

[0009] When a child or young adult presents with a seizure, investigations are normally undertaken in order to investigate the cause. Childhood epilepsy can be caused by many different syndromes and genetic mutations and as such diagnosis for these children may take some time.

[0010] The main symptom of epilepsy is repeated seizures. In order to determine the type of epilepsy or the epileptic syndrome that a patient is suffering from an investigation into the type of seizures that the patient is experiencing is undertaken. Clinical observations and electroencephalography (EEG) tests are conducted and the type(s) of seizures are classified according to the ILEA classification.

[0011] Generalized seizures, where the seizure arises within and rapidly engages bilaterally distributed networks, can be split into six subtypes: tonic-clonic (grand mal) seizures; absence (petit mal) seizures; clonic seizures; tonic seizures; atonic seizures and myoclonic seizures.

[0012] Focal (partial) seizures where the seizure originates within networks limited to only one hemisphere, are also split into sub-categories. Here the seizure is characterized according to one or more features of the seizure, including aura, motor, autonomic and awareness / responsiveness. Where a seizure begins as a localized seizure and rapidly evolves to be distributed within bilateral networks this seizure is known as a bilateral convulsive seizure, which is the proposed terminology to replace secondary generalized seizures (generalized seizures that have evolved from focal seizures and are no longer remain localized).

[0013] Focal seizures where the subject's awareness / responsiveness is altered are referred to as focal seizures with impairment and focal seizures where the awareness or responsiveness of the subject is not impaired are referred to as focal seizures without impairment.

[0014] PCDH19 Epilepsy is a rare X-linked epilepsy syndrome characterized by early onset seizures, cognitive and sensory delays, and behavioral problems. It is caused by a mutation in the PCDH19 gene which codes for protocadherin 19, a protein that plays an important role in communication of brain cells.

[0015] Seizure onset is typically between 3 months to 3 years old and they may become less frequent in later childhood and adolescence. They tend to occur in clusters in the

beginning and can vary significantly, with a duration of days to weeks in some children. Cognitive and intellectual disabilities can range from mild to severe. Despite seizure clusters some children may have normal development and cognitive function.

[0016] Other symptoms that may arise are aggression; attention problems; anxiety; OCD; autistic spectrum features; depression; psychosis. Symptoms noted in some children include fine and gross motor delays; language delay; sensory integration difficulties; sleep problems; low motor tone; constipation; apnea with seizures.

[0017] Seizure medication is the first line of treatment to prevent seizures and seizure clusters. However, the seizures are very difficult to control with medicines during the early years of life and may respond better to medicines over time. Vagal nerve stimulation may be considered in some cases.

[0018] Cannabidiol (CBD), a non-psychoactive derivative from the cannabis plant, has demonstrated anti-convulsant properties in several anecdotal reports, pre-clinical and clinical studies both in animal models and humans. Three randomized control trials showed efficacy of the purified pharmaceutical formulation of CBD in patients with Dravet and Lennox-Gastaut syndrome.

[0019] Based on these three trials, a botanically derived purified CBD preparation was approved by FDA in June 2018 for the treatment of seizures associated with Dravet and Lennox-Gastaut syndromes.

[0020] In 2018 an English newspaper reported on the use of cannabis-based medication to treat a child with PCDH19 Epilepsy. However, the article does not indicate or even suggest the types of seizures that were reduced nor the composition of the cannabis-based medication.[1]

[0021] The applicant has found by way of an open label, expanded-access program that treatment with CBD resulted in a significant reduction in tonic-clonic seizures in a patient with PCDH19 Epilepsy.

BRIEF SUMMARY OF THE DISCLOSURE

[0022] In accordance with a first aspect of the present invention there is provided a cannabidiol (CBD) preparation for use in the treatment of PCDH19 Epilepsy.

[0023] In a further embodiment, the seizures associated with PCDH19 Epilepsy are tonic-clonic seizures.

[0024] In a further embodiment, the CBD preparation comprises greater than 95% (w/w) CBD and not more than 0.15% (w/w) tetrahydrocannabinol (THC).

[0025] Preferably the CBD preparation comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) other cannabinoids, wherein the less than or equal to 2%

(w/w) other cannabinoids comprise the cannabinoids tetrahydrocannabinol (THC); cannabidiol-C1 (CBD-C1); cannabidivarin (CBDV); and cannabidiol-C4 (CBD-C4), and wherein the THC is present as a mixture of trans-THC and cis-THC.

[0026] Preferably the CBD preparation is used in combination with one or more concomitant anti-epileptic drugs (AED).

[0027] Preferably the one or more AED is selected from the group consisting of: levetiracetam, clobazam, topiramate, gabapentin and phenytoin.

[0028] In one embodiment the CBD is present is isolated from cannabis plant material. Preferably at least a portion of at least one of the cannabinoids present in the CBD preparation is isolated from cannabis plant material.

[0029] In a further embodiment the CBD is present as a synthetic preparation. Preferably at least a portion of at least one of the cannabinoids present in the CBD preparation is prepared synthetically.

[0030] Preferably the dose of CBD is greater than 5 mg/kg/day. More preferably the dose of CBD is 20 mg/kg/day. More preferably the dose of CBD is 25 mg/kg/day. More preferably the dose of CBD is 50 mg/kg/day.

[0031] In accordance with a second aspect of the present invention there is provided a method of treating seizures associated with PCDH19 Epilepsy comprising administering a cannabidiol (CBD) preparation to the subject in need thereof.

DEFINITIONS

[0032] Definitions of some of the terms used to describe the invention are detailed below:

[0033] Over 100 different cannabinoids have been identified, see for example, Handbook of Cannabis, Roger Pertwee, Chapter 1, pages 3 to 15. These cannabinoids can be split into different groups as follows: Phytocannabinoids; Endocannabinoids and Synthetic cannabinoids (which may be novel cannabinoids or synthetically produced phytocannabinoids or endocannabinoids).

[0034] "Phytocannabinoids" are cannabinoids that originate from nature and can be found in the cannabis plant. The phytocannabinoids can be isolated from plants to produce a highly purified extract or can be reproduced synthetically.

[0035] "Highly purified cannabinoids" are defined as cannabinoids that have been extracted from the cannabis plant and purified to the extent that other cannabinoids and non-cannabinoid components that are co-extracted with the cannabinoids have been removed, such that the

highly purified cannabinoid is greater than or equal to 95% (w/w) pure.

[0036] "Synthetic cannabinoids" are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.

[0037] Phytocannabinoids can be obtained as either the neutral (decarboxylated form) or the carboxylic acid form depending on the method used to extract the cannabinoids. For example, it is known that heating the carboxylic acid form will cause most of the carboxylic acid form to decarboxylate into the neutral form.

[0038] "Treatment-resistant epilepsy" (TRE) or "intractable epilepsy" is defined as per the ILAE guidance of 2009 as epilepsy that is not adequately controlled by trials of one or more AED.

[0039] "Tonic-clonic seizures" consist of two phases: the tonic phase and the clonic phase. In the tonic phase the body becomes entire rigid, and in the clonic phase there is uncontrolled jerking. Tonic-clonic seizures may or may not be preceded by an aura, and are often followed by headache, confusion, and sleep. They may last mere seconds or continue for several minutes. These seizures are also known as a grand mal seizure.

DETAILED DESCRIPTION

PREPARATION OF HIGHLY PURIFIED CBD EXTRACT

[0040] The following describes the production of the highly-purified (>95% w/w) cannabidiol extract which has a known and constant composition.

[0041] In summary the drug substance used is a liquid carbon dioxide extract of high-CBD containing chemotypes of *Cannabis sativa* L. which had been further purified by a solvent crystallization method to yield CBD. The crystallisation process specifically removes other cannabinoids and plant components to yield greater than 95% CBD. Although the CBD is highly purified because it is produced from a cannabis plant rather than synthetically there is a small number of other cannabinoids which are co-produced and co-extracted with the CBD. Details of these cannabinoids and the quantities in which they are present in the medication are as described in Table A below.

Table A: Composition of highly purified CBD extract

Cannabinoid	Concentration
CBD	> 95% w/w
CBDA	NMT 0.15% w/w
CBDV	NMT 1.0% w/w
Δ^9 THC	NMT 0.15% w/w

CBD-C4	NMT 0.5% w/w

> – greater than

NMT – not more than

PREPARATION OF BOTANICALLY DERIVED PURIFIED CBD

[0042] The following describes the production of the botanically derived purified CBD which comprises greater than or equal to 98% w/w CBD and less than or equal to other cannabinoids was used in the open label, expanded-access program described in Example 1 below.

[0043] In summary the drug substance used in the trials is a liquid carbon dioxide extract of high-CBD containing chemotypes of *Cannabis sativa* L. which had been further purified by a solvent crystallization method to yield CBD. The crystallisation process specifically removes other cannabinoids and plant components to yield greater than 95% CBD w/w, typically greater than 98% w/w.

[0044] The *Cannabis sativa* L. plants are grown, harvested, and processed to produce a botanical extract (intermediate) and then purified by crystallization to yield the CBD (botanically derived purified CBD).

[0045] The plant starting material is referred to as Botanical Raw Material (BRM); the botanical extract is the intermediate; and the active pharmaceutical ingredient (API) is CBD, the drug substance.

[0046] All parts of the process are controlled by specifications. The botanical raw material specification is described in Table B and the CBD API is described in Table C.

Table B: CBD botanical raw material specification

Test	Method	Specification
Identification: -A -B -C	 Visual TLC HPLC/UV	 Complies Corresponds to standard (for CBD & CBDA) Positive for CBDA
Assay: CBDA + CBD	In-house (HPLC/UV)	NLT 90% of assayed cannabinoids by peak area
Loss on Drying	Ph.Eur.	NMT 15%
Aflatoxin	UKAS method	NMT 4ppb
Microbial: - TVC - Fungi - E.coli	Ph.Eur.	NMT 10^7cfu/g NMT 10^5cfu/g NMT 10^2cfu/g
Foreign Matter:	Ph.Eur.	NMT 2%
Residual Herbicides and Pesticides	Ph.Eur.	Complies

Table C: Specification of an exemplary botanically derived purified CBD preparation

Test	Test Method	Limits
Appearance	Visual	Off-white / pale yellow crystals
Identification A	HPLC-UV	Retention time of major peak corresponds to certified CBD Reference Standard
Identification B	GC-FID/MS	Retention time and mass spectrum of major peak corresponds to certified CBD Reference Standard
Identification C	FT-IR	Conforms to reference spectrum for certified CBD Reference Standard
Identification D	Melting Point	65 - 67°C
Identification E	Specific Optical Rotation	Conforms with certified CBD Reference Standard; -110° to -140° (in 95% ethanol)
Total Purity	Calculation	≥ 98.0%
Chromatographic Purity 1	HPLC-UV	≥ 98.0%
Chromatographic Purity 2	GC-FID/MS	≥ 98.0 %
CBDA CBDV THC CBD-C4	HPLC-UV	NMT 0.15% w/w NMT 1.0% w/w NMT 0.1% w/w NMT 0.5% w/w
Residual Solvents: Alkane Ethanol	GC	 NMT 0.5% w/w NMT 0.5% w/w
Residual Water	Karl Fischer	NMT 1.0% w/w

[0047] The purity of the botanically derived purified CBD preparation was greater than or equal to 98%. The botanically derived purified CBD includes THC and other cannabinoids, e.g., CBDA, CBDV, CBD-C1, and CBD-C4.

[0048] Distinct chemotypes of the *Cannabis sativa* L. plant have been produced to maximize the output of the specific chemical constituents, the cannabinoids. Certain chemovars produce predominantly CBD. Only the (-)-trans isomer of CBD is believed to occur naturally. During purification, the stereochemistry of CBD is not affected.

Production of CBD botanical drug substance

[0049] An overview of the steps to produce a botanical extract, the intermediate, are as follows:

a) Growing
b) Direct drying
c) Decarboxylation
d) Extraction - using liquid CO_2
e) Winterization using ethanol
f) Filtration

g) Evaporation

[0050] High CBD chemovars were grown, harvested, dried, baled and stored in a dry room until required. The botanical raw material (BRM) was finely chopped using an Apex mill fitted with a 1 mm screen. The milled BRM was stored in a freezer prior to extraction.

[0051] Decarboxylation of CBDA to CBD was carried out using heat. BRM was decarboxylated at 115ºC for 60 minutes.

[0052] Extraction was performed using liquid CO_2 to produce botanical drug substance (BDS), which was then crystalized to produce the test material. The crude CBD BDS was winterized to refine the extract under standard conditions (2 volumes of ethanol at -20°C for approximately 50 hours). The precipitated waxes were removed by filtration and the solvent was removed to yield the BDS.

Production of botanically derived purified CBD preparation

[0053] The manufacturing steps to produce the botanically derived purified CBD preparation from BDS were as follows:

a) Crystallization using C_5-C_{12} straight chain or branched alkane
b) Filtration
c) Vacuum drying

[0054] The BDS produced using the methodology above was dispersed in C_5-C_{12} straight chain or branched alkane. The mixture was manually agitated to break up any lumps and the sealed container then placed in a freezer for approximately 48 hours. The crystals were isolated via vacuum filtration, washed with aliquots of cold C_5-C_{12} straight chain or branched alkane, and dried under a vacuum of <10mb at a temperature of 60°C until dry. The botanically derived purified CBD preparation was stored in a freezer at -20°C in a pharmaceutical grade stainless steel container, with FDA food grade approved silicone seal and clamps.

Physicochemical properties of the botanically derived purified CBD

[0055] The botanically derived purified CBD used in the clinical trial described in the invention comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) of other cannabinoids. The other cannabinoids present are THC at a concentration of less than or equal to 0.1% (w/w); CBD-C1 at a concentration of less than or equal to 0.15% (w/w); CBDV at a concentration of less than or equal to 0.8% (w/w); and CBD-C4 at a concentration of less than or equal to 0.4% (w/w).

[0056] The botanically derived purified CBD used additionally comprises a mixture of both trans-THC and cis-THC. It was found that the ratio of the trans-THC to cis-THC is altered and can be controlled by the processing and purification process, ranging from 3.3:1 (trans-THC:cis-THC) in its unrefined decarboxylated state to 0.8:1 (trans-THC:cis-THC) when highly purified.

[0057] Furthermore, the cis-THC found in botanically derived purified CBD is present as a mixture of both the (+)-cis-THC and the (-)-cis-THC isoforms.

[0058] Clearly a CBD preparation could be produced synthetically by producing a composition with duplicate components.

[0059] Example 1 below describes the use of a botanically derived purified CBD in an open label, expanded-access program to investigate the clinical efficacy and safety of purified pharmaceutical cannabidiol formulation (CBD) in the treatment of PCDH19 Epilepsy.

EXAMPLE 1: CLINICAL EFFICACY AND SAFETY OF PURIFIED PHARMACEUTICAL CANNABIDIOL (CBD) IN THE TREATMENT OF PATIENTS DIAGNOSED WITH PCDH19 EPILEPSY

Study design

[0060] Subjects were required to be on one or more AEDs at stable doses for a minimum of two weeks prior to baseline and to have stable vagus nerve stimulation (VNS) settings and ketogenic diet ratios for a minimum of four weeks prior to baseline.

[0061] Patients were administered botanically derived purified CBD in a 100 mg/mL sesame oil-based solution.

[0062] A maximum dose of 50 mg/kg/day could be utilised for patients who were tolerating the medication but had not achieved seizure control; these patients had further weekly titration by 5mg/kg/day.

[0063] There was one patient in this study, who received CBD for 16 weeks. Modifications were made to concomitant AEDs as per clinical indication.

[0064] Seizure frequency, intensity, and duration were recorded by caregivers in a diary during a baseline period of at least 28 days. Changes in seizure frequency relative to baseline were calculated after at least 2 weeks and at defined timepoints of treatment.

Statistical Methods:

[0065] Patients may be defined as responders if they had more than 50% reduction in seizure frequency compared to baseline. The percent change in seizure frequency was calculated as follows:

$$\% \text{ change in seizure frequency} = \frac{((\text{weekly seizure frequency } \textit{time interval}) - (\text{weekly seizure frequency } \textit{Baseline}))}{(\text{weekly seizure frequency } \textit{Baseline})} \times 100$$

[0066] The percent change of seizure frequency may be calculated for any time interval where seizure number has been recorded. For the purpose of this example the percent change of seizure frequency for the end of the treatment period was calculated as follows:

$$\% \text{ reduction in seizure frequency} = \frac{((\text{weekly seizure frequency } \textit{Baseline}) - (\text{weekly seizure frequency } \textit{End}))}{(\text{weekly seizure frequency } \textit{Baseline})} \times 100$$

Results

Patient description

[0067] One patient enrolled in the open label, expanded-access program was diagnosed with PCDH19 Epilepsy. This patient experienced tonic-clonic seizures and was taking several concomitant AEDs.

[0068] The patient was 16 years old and she was female as detailed in Table 1 below.

Table 1: Patient demographics, seizure type and concomitant medication

Patient Number	Age (years)	Sex	Seizure types	Concomitant AEDs
1	16.20	F	Tonic-clonic	CLB, LEV, TPM, GBP, PHT

LEV = levetiracetam, CLB = clobazam, TPM = topiramate, GBP = gabapentin, PHT = phenytoin

Study medication and concomitant medications

[0069] The patient on the study was titrated up to 25 mg/kg/day of CBD.

[0070] At the time of starting CBD the patient was on five concomitant AEDs.

Clinical changes

[0071] Table 2 illustrates the seizure frequency for the patient as well as the dose of CBD given.

Table 2: Seizure frequency data for Patient 1

Patient 1		
Time	**Seizure Type**	**Dose CBD (mg/kg/day)**
	Tonic-clonic	
Baseline	280.0	-
4 weeks	120.0	15.0
8 weeks	160.0	25.0
16 weeks	140.0	25.0

[0072] Patient 1 was treated for 16 weeks and experienced a 50% reduction in tonic-clonic seizures over the treatment period.

[0073] Overall, the patient reported a reduction of 50% in seizures over period of treatment with CBD. CBD was effective in reducing the frequency of tonic-clonic seizures.

Conclusions

[0074] These data indicate that CBD was able to significantly reduce the number of seizures associated with PCDH19 Epilepsy. Clearly the treatment is of significant benefit in this difficult to treat epilepsy syndrome given the high response rate experienced in the patient.

[0075] In conclusion, this study signifies the use of CBD for treatment of seizures associated with PCDH19 Epilepsy. Seizure types include tonic-clonic seizures for which seizure frequency rate decreased significantly, by 50%.

References

1. Oppenheim. (2018) “Government refuses medical cannabis to six-year-old epileptic boy who had 3,000 seizures in a year.” The Independent. https://www.independent.co.uk/news/uk/home-news/alfie-dingley-home-office-medical-cannabis-denies-seizures-netherlands-a8216596.html

CLAIMS

1. A cannabidiol (CBD) preparation for use in the treatment of seizures associated with PCDH19 Epilepsy.

2. A CBD preparation for use according to claim 1, wherein the seizures associated with PCDH19 Epilepsy are tonic-clonic seizures.

3. A CBD preparation for use according to any of the preceding claims, wherein the CBD preparation comprises greater than 95% (w/w) CBD and not more than 0.15% (w/w) tetrahydrocannabinol (THC).

4. A CBD preparation for use according to any of the preceding claims, wherein the CBD preparation comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) other cannabinoids, wherein the less than or equal to 2% (w/w) other cannabinoids comprise the cannabinoids tetrahydrocannabinol (THC); cannabidiol-C1 (CBD-C1); cannabidivarin (CBDV); and cannabidiol-C4 (CBD-C4), and wherein the THC is present as a mixture of trans-THC and cis-THC.

5. A CBD preparation to any of the preceding claims, wherein the CBD preparation is used in combination with one or more concomitant anti-epileptic drugs (AED).

6. A CBD preparation for use according to claim 5, wherein the one or more AED is selected from the group consisting of: levetiracetam, clobazam, topiramate, gabapentin and phenytoin.

7. A CBD preparation for use according to any of the preceding claims, wherein the CBD is present is isolated from cannabis plant material.

8. A CBD preparation for use according to any of the preceding claims, wherein at least a portion of at least one of the cannabinoids present in the CBD preparation is isolated from cannabis plant material.

9. A CBD preparation for use according to claims 1 to 6, wherein the CBD is present as a synthetic preparation.

10. A CBD preparation for use according to claim 9, wherein at least a portion of at least one of the cannabinoids present in the CBD preparation is prepared synthetically.

11. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is greater than 5 mg/kg/day.

12. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is 20 mg/kg/day.

13. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is 25 mg/kg/day.

14. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is 50 mg/kg/day.

15. A method of treating seizures associated with PCDH19 Epilepsy comprising administering a cannabidiol (CBD) preparation to the subject in need thereof.

Intellectual Property Office

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Claims searched:	1-15	**Date of search:**	16 December 2020

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1-15	Health Europa, 2019, "The fight for getting access to medical cannabis in the UK goes on", healtheuropa.eu, [online], available via https://www.healtheuropa.eu/access-to-medical-cannabis-in-the-uk/93025/ - see whole document
X	1-15	Epilepsy & Behavior, vol. 29, 2013, Porter & Jacobson, "Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy", pages 574-577, available via https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157067/ - see table 1, patient 3
X	1-15	WO2019/045121 A1 (TAKEDA PHARMACEUTICALS CO) - see paragraph [0008]
X	1-15	WO2019/071302 A1 (UNIV SYDNEY) - see page 2, lines 17-20; page 4, lines 11-14; page 15, line 8
Y	1-15	Dev. Med. Child Neurol., vol. 60, 2018, Kurian et al., "Focal cortical malformations in children with early infantile epilepsy and PCDH19 mutations: case report", pages 100-105, available via https://onlinelibrary.wiley.com/doi/full/10.1111/dmcn.13595 - see abstract & introduction
Y	1-15	Brain and Development, vol. 40, 2018, Hausman-Kedem et al., "Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents An observational, longitudinal study", pages 544-551 available via https://d1wqtxts1xzle7.cloudfront.net/61726004/1-s2.0-S0387760418301128-main20200109-85148-zcvf17.pdf?1578557120=&response-content-disposition=inline%3B+filename%3DEfficacy_of_CBD_enriched_medical_cannabi.pdf&Expires=1607961095&Signature=WltOAWby53r0SqQ5upEoij2p8j1W8YVWUP7b7bEkf3OG2zbb
Y	1-15	N. Engl. J. Med., vol. 376, 2017, Devinsky et al., "Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome", pages 2011-2020, available via https://www.nejm.org/doi/full/10.1056/nejmoa1611618 - see abstract

Intellectual Property Office

Y	1-15	Epilepsia, vol. 57, 2016, Hess et al., "Cannabidiol as a new treatment for drug-resistant epilepsyin tuberous sclerosis complex", pages 1617-1624, available via https://onlinelibrary.wiley.com/doi/epdf/10.1111/epi.13499 - see summary
Y	1-15	Epilepsia, vol. 60, 2019, Thiele et al., "Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study", pages 419-428, available via https://pubmed.ncbi.nlm.nih.gov/30740695/ - see summary
Y	1-15	Epilepsia, vol. 58, 2018, Rosenberg et al., "Quality of Life of Childhood Epilepsy (QOLCE) in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol (CBD)", pages 96-100, available via https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5568670/ - see 'Changes in seizure in frequency'

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

The following online and other databases have been used in the preparation of this search report

WPI, EPODOC, Patent Fulltext, INTERNET, BIOSIS, MEDLINE, XPESP, NPL, XPOAC

International Classification:

Subclass	Subgroup	Valid From
A61K	0031/05	01/01/2006
A61K	0036/185	01/01/2006
A61P	0025/08	01/01/2006
A61P	0025/10	01/01/2006
A61P	0025/12	01/01/2006