(12) UK Patent Application (19) GB (11) 2531282 (13) A

(43) Date of A Publication 20.04.2016

(21) Application No: 1418171.3

(22) Date of Filing: 14.10.2014

(71) Applicant(s):
GW Pharma Limited
Sovereign House, Histon, Cambridge, CB24 9BZ, United Kingdom

(72) Inventor(s):
Geoffrey Guy
Stephen Wright
Alice Mead
Orrin Devinsky

(74) Agent and/or Address for Service:
HGF Limited
Document Handling - HGF - (Manchester),
1 City Walk, LEEDS, LS11 9DX, United Kingdom

(51) INT CL:
A61K 31/05 (2006.01) ***A61K 36/185*** (2006.01)
A61P 25/08 (2006.01)

(56) Documents Cited:
Epilepsy & Behavior, vol. 29, No. 3, 2013, pages 574-577
http://www.gwpharm.com/GW%20Pharmaceuticals%20Provides%20Update%20on%20Orphan%20Program%20in%20Childhood%20Epilepsy%20for%20Epidiolex.aspx [Available online 14 November 2013]
Epilepsia, vol. 55, No. 6, 2014, pages 783-786
http://www.gwpharm.com/LGS%20Orphan%20Designation.aspx [Available online 28 February 2014]
http://web.archive.org/web/20100902130020/http://www.cannabis-med.org/studies/ww_en_db_study_show.php?s_id=173&&search_pattern=EPILEPSY [Available online 2 September 2010]
https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/1868979# [Available online 2014]

(58) Field of Search:
INT CL **A61K, A61P**
Other: **CAS ONLINE, EPODOC, WPI, MEDLINE, BIOSIS, INTERNET**

(54) Title of the Invention: **Use of cannabinoids in the treatment of epilepsy**
Abstract Title: **Cannabidiol for use in the treatment of treatment-resistant epilepsy**

(57) Cannabidiol (CBD) for use in the treatment of epilepsy, wherein the epilepsy is treatment-resistant epilepsy (TRE), and wherein the epilepsy to be treated is characterised by atonic seizures, is provided. Preferably the atonic seizures to be treated are in patients diagnosed with Lennox-Gastaut syndrome, tuberous sclerosis complex, Dravet syndrome, Doose syndrome, CDKL5 and Dup15q. The CBD is preferably for use in combination with one or more concomitant anti-epileptic drugs (AED), in particular clobazam, levetiracetam, topiramate, stiripentol, phenobarbital, lacsamide, valproic acid, zonisamide, perampanel and fosphenytoin, wherein the dose of the anti-epileptic drug/s that is/are used in combination with CBD is reduced. Preferably the CBD is present as a highly purified extract of cannabis which comprises at least 98% (w/w) CBD. Preferably the extract further comprises up to 1% CBDV (cannabidivarin) and less than 0.15% THC (tetrahydrocannabinol). Preferably the dose of CBD is from 5mg/kg/day to 25mg/kg/day.

GB 2531282 A

USE OF CANNABINOIDS IN THE TREATMENT OF EPILEPSY

[0001] The present invention relates to the use of cannabidiol (CBD) for the reduction of atonic seizures in the treatment of intractable epilepsy. In one embodiment the patients suffering from intractable epilepsy are children and young adults. CBD appears particularly effective in reducing atonic seizures in patients suffering from intractable epilepsy in etiologies including: Lennox-Gastaut Syndrome; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; CDKL5 and Dup15q where atonic seizures are a symptom.

[0002] In these patients the reduction of atonic seizures has surprisingly been shown to be greater than 50%, through 70% to greater than 90% in a significant number of patients in comparison to patients with other convulsive seizures such as partial seizures. Indeed a significant number of patients have been atonic seizure free at the end of a three months treatment period.

[0003] Preferably the CBD used is in the form of a highly purified extract of cannabis such that the CBD is present at greater than 98% of the total extract (w/w) and the other components of the extract are characterised. In particular the cannabinoid tetrahydrocannabinol (THC) has been substantially removed, to a level of not more than 0.15% (w/w) and the propyl analogue of CBD, cannabidivarin, (CBDV) is present in amounts of up to 1%. Alternatively, the CBD may be a synthetically produced CBD.

[0004] In use the CBD is used concomitantly with one or more other anti-epileptic drugs (AED). Alternatively 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. Where the CBD is formulated for administration separately, sequentially or simultaneously it may be provided as a kit or together with instructions to administer the one or more components in the manner indicated. It may also be used as the sole medication, i.e. as a monotherapy.

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 described below.

[0011] Focal (partial) seizures which only involve a localized part of the brain. This can be subdivided into three categories: Simple Partial Seizures, where consciousness is not impaired; Complex Partial Seizures (also known as temporal lobe seizures), where consciousness is impaired; and Partial Seizures evolving to Secondary Generalised Seizures, where the seizures begin in a localized part of the brain and then evolve to encompass the whole brain.

[0012] Generalised seizures involve the whole brain and can also be subdivided into types: Absence (petit mal) Seizures; Myoclonic Seizures; Clonic Seizures; Tonic Seizures; Tonic-Clonic (grand mal) seizures; and Atonic Seizures.

[0013] Atonic seizures involve the loss of muscle tone, causing the person to fall to the ground. These are sometimes called 'drop attacks' and are usually brief (less than 15 seconds). Atonic seizures can occur without warning while standing, sitting and walking and the patient often suffers from trauma due to falling.

[0014] Atonic seizures are often associated with Lennox-Gastaut Syndrome but also occur, and may be symptomatic of other types of epileptic syndromes including: Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; CDKL5 and Dup15q.

[0015] Epileptic syndromes such as Lennox-Gastaut Syndrome often present with many different types of seizure and identifying the types of seizure that a patient is suffering from is important as many of the standard AED's are targeted to treat a given seizure type these can be both generalised and partial seizure types.

[0016] The first line treatment for atonic seizures usually comprises a broad spectrum AED, such as sodium valproate often as an adjunctive treatment with lamotrigine. Other AED that may be considered include rufinamide and topiramate.

[0017] Other AED such as carbamezapine, gabapentin, oxcarbazepine, pregabalin, tiagabineor vigabatrin are contra-indicated in atonic seizures.

[0018] Common AED defined by their mechanisms of action are described in the following tables:

[0019] **Examples of narrow spectrum AED**

Narrow-spectrum AED	**Mechanism**	**Indication**
Phenytoin	Sodium channel	Complex partial Tonic-clonic
Phenobarbital	GABA / Calcium channel	Partial seizures Tonic-clonic
Carbamazepine	Sodium channel	Partial seizures Tonic-clonic Mixed seizures
Oxcarbazepine	Sodium channel	Partial seizures Tonic-clonic Mixed seizures
Gabapentin	Calcium channel	Partial seizures Mixed seizures
Pregabalin	Calcium channel	Adjunct therapy for partial seizures with or without secondary generalisation
Lacosamide	Sodium channel	Adjunct therapy for partial seizures
Vigabatrin	GABA	Secondarily generalized tonic-clonic seizures Partial seizures Infantile spasms due to West syndrome

[0020] **Examples of broad spectrum AED**

Broad-spectrum AED	**Mechanism**	**Indication**
Valproic acid	GABA / Sodium channel	First-line treatment for tonic-clonic seizures, absence seizures and myoclonic seizures Second-line treatment for partial seizures and infantile spasms. Intravenous use in status epilepticus
Lamotrigine	Sodium channel	Partial seizures Tonic-clonic Seizures associated with Lennox-Gastaut syndrome
Topiramate	GABA / Sodium channel	Seizures associated with Lennox-Gastaut syndrome
Zonisamide	GABA / Calcium /Sodium channel	Adjunctive therapy in adults with partial-onset seizures Infantile spasm Mixed seizure Lennox-Gastaut syndrome Myoclonic Generalised tonic-clonic seizure
Levetiracetam	Calcium channel	Partial seizures Adjunctive therapy for partial, myoclonic and tonic-clonic seizures
Clonazepam	GABA	Typical and atypical absences Infantile myoclonic Myoclonic seizures Akinetic seizures
Rufinamide	Sodium channel	Adjunctive treatment of partial

		seizures associated with Lennox-Gastaut syndrome

[0021] Examples of AED used specifically in childhood epilepsy

AED	Mechanism	Indication
Clobazam	GABA	Adjunctive therapy in complex partial seizures Status epilepticus Myoclonic Myoclonic-absent Simple partial Complex partial Absence seizures Lennox-Gastaut syndrome
Stiripentol	GABA	Severe myoclonic epilepsy in infancy (Dravet syndrome)

[0022] Over the past forty years there have been a number of animal studies on the use of the non-psychoactive cannabinoid cannabidiol (CBD) to treat seizures. For example, Consroe *et al.*, (1982) determined that CBD was able to prevent seizures in mice after administration of pro-convulsant drugs or an electric current.

[0023] Studies in epileptic adults have also occurred in the past forty years with CBD. Cunha *et al.* reported that administration of CBD to eight adult patients with generalized epilepsy resulted in a marked reduction of seizures in 4 of the patients (Cunha *et al.*, 1980).

[0024] A study in 1978 provided 200 mg/day of pure CBD to four adult patients, two of the four patients became seizure free, whereas in the remainder seizure frequency was unchanged (Mechoulam and Carlini, 1978).

[0025] In contrast to the studies described above, an open label study reported that 200 mg / day of pure CBD was ineffective in controlling seizures in twelve institutionalized adult patients (Ames and Cridland, 1986).

[0026] In the past forty years of research there have been over thirty drugs approved for the treatment of epilepsy none of which are cannabinoids. Indeed, there appears to have been a prejudice against cannabinoids, possible due to the scheduled nature of these compounds and / or the fact that THC, which is a known psychoactive, has been ascribed as a pro-convulsant (Consroe *et al.*, 1977).

[0027] A paper published recently suggested that cannabidiol-enriched cannabis may be efficacious in the treatment of epilepsy. Porter and Jacobson (2013) report on a parent survey conducted via a Facebook group which explored the use of cannabis which was enriched with CBD in children with treatment-resistant epilepsy. It was found that sixteen of the 19 parents surveyed reported an improvement in their child's epilepsy. The children surveyed for this paper were all taking cannabis that was purported to contain CBD in a high concentration although the amount of CBD present and the other constituents including THC were not known. Indeed, whilst CBD levels ranged from 0.5 to 28.6 mg/kg/day (in those extracts tested), THC levels as high as 0.8 mg/kg/day were reported.

[0028] Providing children with TRE with a cannabis extract that comprises THC, which has been described as a pro-convulsant (Consroe *et al.*, 1977), in even small amounts, let alone at a potentially psychoactive dose of 0.8 mg/kg/day, is extremely dangerous and as such there is a real need to determine whether CBD is in fact efficacious.

[0029] To date there have been no controlled trials of CBD in children and young adults with intractable epilepsy.

BRIEF SUMMARY OF THE DISCLOSURE

[0030] In accordance with a first aspect of the present invention there is provided cannabidiol (CBD) for use in the treatment of epilepsy, wherein the epilepsy is a treatment-resistant epilepsy (TRE), and wherein the epilepsy to be treated is characterised by atonic seizures.

[0031] In one embodiment the CBD is for use in combination with one or more concomitant anti-epileptic drugs (AED).

[0032] Preferably the atonic seizures to be treated are in patients diagnosed with: Lennox-Gastaut Syndrome, Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; CDKL5 and Dup15q.

[0033] Most preferably the treatment-resistant epilepsy is Lennox-Gastaut Syndrome.

[0034] In a further embodiment the CBD is present as a highly purified extract of cannabis which comprises at least 98% (w/w) CBD. Preferably the extract comprises less than 0.15% THC. More preferably the extract further comprises up to 1% CBDV.

[0035] In a further embodiment of the invention the one or more AED is selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

[0036] Preferably the number of different anti-epileptic drugs that are used in combination with the CBD is reduced. Alternatively the dose of anti-epileptic drugs that are used in combination with the CBD is reduced.

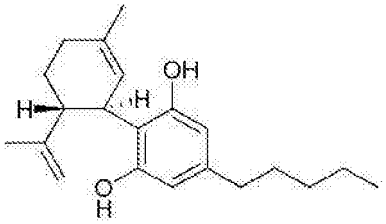
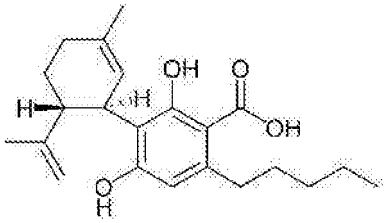
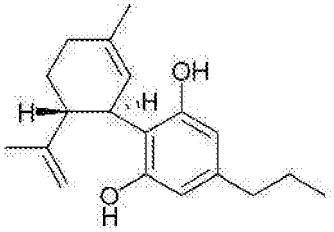
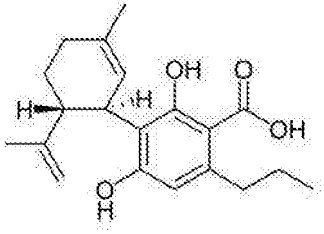
[0037] Preferably the dose of CBD is from 5 mg/kg/day to 25 mg/kg/day.

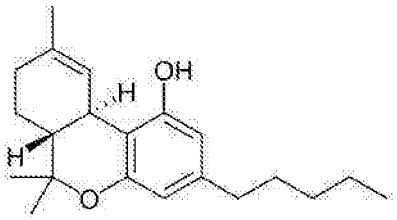
[0038] In accordance with a second aspect of the present invention there is provided a method of treating treatment-resistant epilepsy comprising administering cannabidiol (CBD) to a patient, wherein the epilepsy to be treated is characterised by atonic seizures.

DEFINITIONS

[0039] Definitions of some of the terms used to describe the invention are detailed below:

[0040] The cannabinoids described in the present application are listed below along with their standard abbreviations.

CBD	Cannabidiol	
CBDA	Cannabidiolic acid	
CBDV	Cannabidivarin	
CBDVA	Cannabidivarinic acid	

THC	Tetrahydrocannabinol	

[0041] The table above is not exhaustive and merely details the cannabinoids which are identified in the present application for reference. So far over 60 different cannabinoids have been identified and 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).

[0042] "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.

[0043] "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 98% (w/w) pure.

[0044] "Synthetic cannabinoids" are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.

[0045] 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.

[0046] "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.

[0047] "Childhood epilepsy" refers to the many different syndromes and genetic mutations that can occur to cause epilepsy in childhood. Examples of some of these are as follows: Dravet Syndrome; Myoclonic-Absence Epilepsy; Lennox-Gastaut syndrome; Generalized Epilepsy of unknown origin; CDKL5 mutation; Aicardi syndrome; bilateral polymicrogyria; Dup15q; SNAP25; and febrile infection related epilepsy syndrome (FIRES); benign rolandic epilepsy; juvenile myoclonic epilepsy; infantile spasm (West syndrome); and Landau-Kleffner syndrome. The list above is non-exhaustive as many different childhood epilepsies exist.

[0048] "Atonic Seizures" are defined as a convulsive type of epileptic seizure which causes the muscles to relax and the patient to flop or fall.

DETAILED DESCRIPTION

PREPARATION OF HIGHLY PURIFIED CBD EXTRACT

[0049] The following describes the production of the highly-purified (>98% w/w) cannabidiol extract which has a known and constant composition which was used for the expanded access trials described in Examples below.

[0050] 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 98% CBD.

[0051] 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 (drug substance).

[0052] 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.

[0053] Both the botanical starting material and the botanical extract are controlled by specifications. The drug substance specification is described in Table 1 below.

Table 1. CBD Specification

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%

Test	Test Method	Limits
Chromatographic Purity 2	GC-FID/MS	≥ 98.0 %
Other Cannabinoids: - CBDA - CBDV - Δ^9 THC - CBD-C4	HPLC-UV	 NMT 0.15% w/w NMT 1.0% w/w NMT 0.15% 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

NMT- Not more than

[0054] The purity of the CBD drug substance achieved is greater than 98%. The other cannabinoids which may occur in the extract are: CBDA, CBDV, CBD-C4 and THC.

[0055] Distinct chemotypes of *Cannabis sativa* L. plant have been produced to maximize the output of the specific chemical constituents, the cannabinoids. One type of plant produces predominantly CBD. Only the (–)-trans isomer occurs naturally, furthermore during purification the stereochemistry of CBD is not affected.

Production of the Intermediate

[0056] An overview of the steps to produce a botanical extract, the intermediate, are as follows:

1. Growing
2. Decarboxylation
3. Extraction No.1 - using liquid CO_2
4. Extraction No.2 - 'winterization' using ethanol
5. Filtration
6. Evaporation

[0057] High CBD chemovars were grown, harvested and dried and stored in a dry room until required. The botanical raw material (BRM) was finely chopped using an Apex mill fitted with a 1mm screen. The milled BRM was stored in a freezer for up to 3 months prior to extraction.

[0058] Decarboxylation of CBDA to CBD was carried out using a large Heraeus tray oven. The decarboxylation batch size in the Heraeus is approximately 15 Kg. Trays were placed in the oven and heated to 105ºC; the BRM took 96.25 minutes to reach 105 ºC. Held at 105ºC for 15 Minutes. Oven then set to 150ºC.; the BRM took 75.7 minutes to reach 150ºC; BRM held at 150ºC for 130 Minutes. Total time in the oven was 380 Minutes, including 45 minutes cooling and 15 Minutes venting.

[0059] Extraction No 1 was performed using liquid CO_2 at 60 bar / 10°C to produce botanical drug substance (BDS) which was used for crystallisation to produce the test material.

[0060] The crude CBD BDS was winterised in Extraction No 2 under standard conditions (2 volumes of ethanol at minus 20°C for around 50 hours). The precipitated waxes were removed by filtration and the solvent evaporated using the rotary evaporator (water bath up to 60°C) to yield the BDS.

Production of the Drug Substance

[0061] The manufacturing steps to produce the drug substance from the intermediate botanical extract are as follows:

1. Crystallization using C5-C12 straight chain or branched alkane
2. Filtration
3. Optional recrystallization from C5-C12 straight chain or branched alkane
4. Vacuum drying

[0062] Intermediate botanical extract (12kg) produced using the methodology above was dispersed in C5-C12 straight chain or branched alkane (9000 ml, 0.75 vols) in a 30 litre stainless steel vessel.

[0063] The mixture was manually agitated to break up any lumps and the sealed container then placed in a freezer for approximately 48 hours.

[0064] The crystals were isolated by vacuum filtration, washed with aliquots of cold C5-C12 straight chain or branched alkane (total 12000 ml), and dried under a vacuum of < 10mb at a temperature of 60°C until dry before submitting the drug substance for analysis.

[0065] The dried product was stored in a freezer at minus 20°C in a pharmaceutical grade stainless steel container, with FDA food grade approved silicone seal and clamps.

[0066] Example 1 below describes the use of a highly purified cannabis extract comprising cannabidiol (CBD). Cannabidiol is the most abundant non-psychoactive cannabinoid in the selected chemovar. Previous studies in animals have demonstrated that CBD has anticonvulsant efficacy in multiple species and models.

[0067] Example 1 describes data produced in an expanded access treatment program in children with TRE.

EXAMPLE 1: EFFICACY OF CANNABIDIOL REDUCING ATONIC SEIZURES IN CHILDREN AND YOUNG ADULTS WITH INTRACTABLE EPILEPSY

Materials and Methods

[0068] Thirty-six children and young adults with severe, childhood onset treatment-resistant epilepsy (TRE) were tested with a highly purified extract of cannabidiol (CBD) obtained from a cannabis plant. The participants in the study were part of an expanded access compassionate use program for CBD.

[0069] Of those 36 patients, ten suffered from atonic type seizures. The epileptic syndromes that these 10 patients suffered from were as follows: Lennox-Gastaut Syndrome; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; CDKL5 and Dup15q

[0070] All patients entered a baseline period of 4 weeks when parents/caregivers kept prospective seizure diaries, noting all countable motor seizure types.

[0071] The patients then received a highly purified CBD extract (greater than 98% CBD w/w) in sesame oil, of known and constant composition, at a dose of 5 mg/kg/day in addition to their baseline anti-epileptic drug (AED) regimen.

[0072] The daily dose was gradually increased by 2 to 5mg/kg increments until intolerance occurred or a maximum dose of 25 mg/kg/day was achieved.

[0073] Patients were seen at regular intervals of 2-4 weeks. Laboratory testing for hematologic, liver, kidney function, and concomitant AED levels was performed at baseline, and after 4, 8, 12 and 16 weeks of CBD therapy.

Results

[0074] There were 36 children and young adult patients who received at least 4 months of treatment all of whom suffered from treatment-resistant epilepsy.

[0075] All patients were taking at least two concomitant anti-epileptic drugs. These included clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide. The average number of concomitant antiepileptic drugs being taken was 2.7. The majority took either clobazam and / or valproic acid.

[0076] The percentage change from baseline in the number and type of seizures after 16 weeks treatment are summarized in Table 2 below.

Table 2. Changes in Seizure Frequency with CBD Therapy after 16 weeks of treatment

	Atonic Seizures (n=10)	Partial seizures (n=10)	All convulsive seizures including atonic (n=32)	All convulsive seizures excluding atonic (n=22)	Total seizures (convulsive and non-convulsive)

					(n=36)
Responder rate (>50% reduction)	70%	40%	56%	50%	58%
Responder rate (>70% reduction)	60%	20%	32%	19%	31%
Responder rate (>90% reduction)	30%	10%	26%	24%	19%
Seizure free	20%	10%	16%	14%	11%

[0077] Table 2 shows that after 4 months of therapy, a remarkable 70% of patients had an equal to or greater than >50% reduction in atonic seizures. When this figure is compared to those obtaining a 50% reduction in partial seizures, where only 40% of patients obtained greater than 50% reduction these data infer that the CBD is very effective at reducing this type of seizure.

[0078] Indeed the responder rates across the range of >50%, >70% and >90% are significantly higher for atonic seizures than partial seizures.

[0079] When the responder rates for atonic seizures are compared with the group "all convulsive seizures, including atonic seizures" again a higher rate is observed in the atonic group. The >70% reduction in seizures group demonstrates an almost double the number of patients able to benefit from a greater than 70% reduction in seizures than in the group which comprises all convulsive seizures. Again these data demonstrate the effectiveness of the CBD in treating this particular type of seizure.

[0080] Furthermore when the responder rates for the atonic seizure group are compared with the group "all convulsive seizures, excluding atonic seizures", where those patients with atonic seizures have been excluded from the data set, an even higher effect is observed. In the >70% responder rate group 60% of atonic patients obtain a greater than 70% reduction in seizures in comparison to less than 20% of other patients suffering from convulsive seizures.

[0081] Importantly 10% of the patients were entirely free from seizures at the four month stage. This is particularly impressive due to the intractable nature of the epilepsy that these children and young adults are suffering from.

Conclusions

[0082] These data indicate that CBD significantly reduces the number of atonic type seizures in a high proportion of patients that do not respond well to existing AED.

[0083] It was surprising that in this group of patients which are treatment-resistant such a high number were able to gain an effect. The fact that over two thirds of the patients (70%) benefitted from at least a fifty percent reduction in the number of atonic seizures that they suffered from was remarkable.

[0084] Furthermore, nearly a third (30%) of patients, whose seizures were not controlled with at least two anti-epileptic drugs, experienced a reduction of 90% of the number of seizures they were experiencing and 20% were completely seizure free at the end of the 4 month trial period.

References:

Ames FR and Cridland S (1986). “Anticonvulsant effects of cannabidiol.” S Afr Med J 69:14.

Consroe P, Martin P, Eisenstein D. (1977). “Anticonvulsant drug antagonism of delta-9-tetrahydrocannabinol induced seizures in rabbits.” Res Commun Chem Pathol Pharmacol. 16:1-13

Consroe P, Benedicto MA, Leite JR, Carlini EA, Mechoulam R. (1982). “Effects of cannabidiol on behavioural seizures caused by convulsant drugs or current in mice.” Eur J Pharmaco. 83: 293-8

Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimental C, Gagliardi R *et al.* (1980). “Chronic administration of cannabidiol to healthy volunteers and epileptic patient.” Pharmacology. 21:175-85

Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011 Apr;52 Suppl 2:3-9.

Eadie, MJ (December 2012). "Shortcomings in the current treatment of epilepsy." *Expert Review of Neurotherapeutics* 12 (12): 1419–27.

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. (2009) “Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies.” *Epilepsia.*

Mechoulam R and Carlini EA (1978). “Toward drugs derived from cannabis.” Die naturwissenschaften 65:174-9.

Porter BE, Jacobson C (December 2013). “Report of a parent survey of cannabidiol-enriched cannabis use in paediatric treatment resistant epilepsy” Epilepsy Behaviour. 29(3) 574-7

Thurman, DJ; Beghi, E; Begley, CE; Berg, AT; Buchhalter, JR; Ding, D; Hesdorffer, DC; Hauser, WA; Kazis, L; Kobau, R; Kroner, B; Labiner, D; Liow, K; Logroscino, G; Medina, MT; Newton, CR; Parko, K; Paschal, A; Preux, PM; Sander, JW; Selassie, A; Theodore, W; Tomson, T; Wiebe, S; ILAE Commission on, Epidemiology (September 2011). "Standards for epidemiologic studies and surveillance of epilepsy." *Epilepsia*. 52 Suppl 7: 2–26

CLAIMS

1. Cannabidiol (CBD) for use in the treatment of epilepsy, wherein the epilepsy is a treatment-resistant epilepsy (TRE), and wherein the epilepsy to be treated is characterised by atonic seizures.

2. CBD for use according to claim 1, wherein the CBD is for use in combination with one or more concomitant anti-epileptic drugs (AED).

3. CBD for use according to claim 1 or claim 2, wherein the atonic seizures to be treated are in patients diagnosed with: Lennox-Gastaut Syndrome, Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; CDKL5 and Dup15q.

4. CBD for use according to claim 3, wherein the treatment-resistant epilepsy is Lennox-Gastaut Syndrome.

5. CBD for use according to any of the preceding claims, wherein the CBD is present as a highly purified extract of cannabis which comprises at least 98% (w/w) CBD.

6. CBD for use according to claim 5 wherein the extract comprises less than 0.15% THC.

7. CBD for use according to claim 5 or 6 wherein the extract further comprises up to 1% CBDV.

8. CBD for use according to claim 2, wherein the one or more AED is selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

9. CBD for use according to any of the preceding claims, wherein the number of different anti-epileptic drugs that are used in combination with the CBD is reduced.

10. CBD for use according to any of the preceding claims, wherein the dose of anti-epileptic drugs that are used in combination with the CBD is reduced.

11. CBD for use according to any of the preceding claims, wherein the dose of CBD is from 5 mg/kg/day to 25 mg/kg/day.

12. A method of treating treatment-resistant epilepsy comprising administering cannabidiol (CBD) to a patient, wherein the epilepsy to be treated is characterised by atonic seizures.

Application No:	GB1418171.3	**Examiner:**	Dr Natalie Cole
Claims searched:	1-12	**Date of search:**	26 June 2015

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	1-3, 5, 6, 8-12	Epilepsia, vol. 55, No. 6, 2014, pages 783-786 MAA et al. "The case for medical marijuana in epilepsy". See whole document especially abstract
X	1-6, 9, 10, 12 at least	http://web.archive.org/web/20100902130020/http://www.cannabis-med.org/studies/ww_en_db_study_show.php?s_id=173&&search_pattern=EPILEPSY [Available online 2 September 2010] PELLICCIA et al. "Treatment with CBD in oily solution of drug-resistant paediatric epilepsies". See whole document [Accessed 22 June 2015]
X	1, 3-6, 11, 12 at least	Epilepsy & Behavior, vol. 29, No. 3, 2013, pages 574-577 PORTER et al. "Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy". See whole document especially abstract and table 1
X	1, 3-6, 11, 12 at least	http://www.gwpharm.com/GW%20Pharmaceuticals%20Provides%20Update%20on%20Orphan%20Program%20in%20Childhood%20Epilepsy%20for%20Epidiolex.aspx [Available online 14 November 2013] "GW Pharmaceuticals provides update on orphan program in childhood epilepsy for Epidiolex". See whole document [Accessed 22 June 2015]
X	1, 3-6, 11, 12 at least	http://www.gwpharm.com/LGS%20Orphan%20Designation.aspx [Available online 28 February 2014] "GW Pharmaceuticals receives orphan drug designation by FDA for Epidiolex in the treatment of Lennox-Gastaut syndrome". See whole document [Accessed 22 June 2015]
X	1, 3, 5, 6, 11, 12	https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/1868979# [Available online 2014] GEFFREY et al. American Epilepsy Society; Annual General Meeting Abstracts: View "Cannabidiol (CBD) treatment for refractory epilepsy in tuberous sclerosis complex (TSC)". See whole document [Accessed 23 June 2015]

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

A61K; A61P

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

CAS ONLINE, EPODOC, WPI, MEDLINE, BIOSIS, INTERNET

International Classification:

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