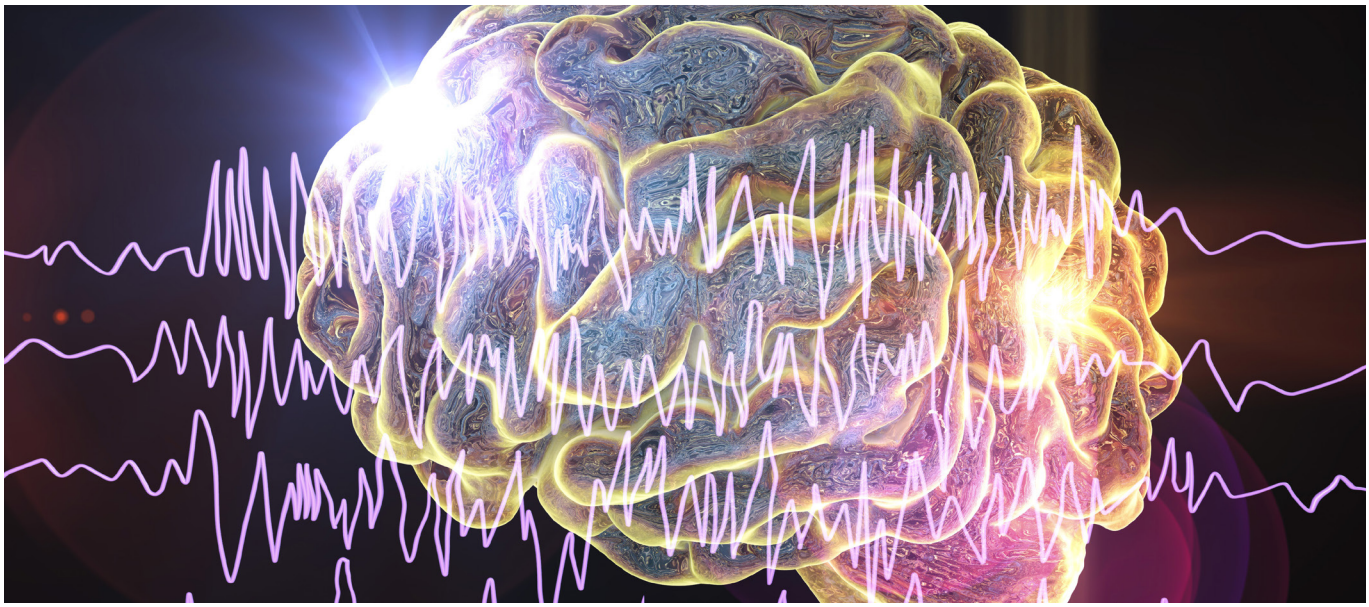
SHARING EXPERIENCE WITH EPIDYOLEX® (CANNABIDIOL) 'GW CBD' – CONTROVERSIES, CHALLENGES AND SOLUTIONS

Highlights of a GW Pharmaceuticals-sponsored Epilepsy Focus webinar held in September 2020



Epidyolex® (cannabidiol) 'GW CBD' is indicated for use in Europe as an adjunctive therapy in conjunction with clobazam for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients ≥2 years of age;[1] it is additionally approved in Northern Ireland and the EU for the adjunctive treatment of seizures associated with tuberous sclerosis complex in patients ≥2 years of age. Please note that the indicated use for GW CBD may differ in your country. The potential benefits and risks of treatment with GW CBD are illustrated in eight diverse case studies of patients with Lennox–Gastaut syndrome or Dravet syndrome.

Initiating GW CBD treatment for patients with epilepsy

Professor Angela Kaindl presented two cases that may provide insight into factors predicting the response to GW CBD. This first case was **a 6-year-old girl with Lennox–Gastaut syndrome** whose seizures were refractory to most anti-epileptic drugs and who had stopped clobazam as she experienced agitation as a side effect of the treatment. Treatment was initiated with GW CBD 2.2 mg/kg/day in conjunction with clobazam 0.04 mg/kg/day but was stopped after 2 weeks as the patient experienced side effects of agitation, reduced sleep and increased seizure frequency. In contrast, Professor Kaindl's second case was **a 9-year-old boy with Lennox–Gastaut syndrome**. Treatment with clobazam 0.1 mg/kg/day was initiated, resulting in a reduction in seizure frequency. Clobazam was up-titrated to 0.2 mg/kg/day and GW CBD initiated 1 week later at 2.2 mg/kg/day, and GW CBD subsequently increased every week by 2–5 mg/kg/day to the target dose of 20 mg/kg/day. Add-on GW CBD treatment resulted in fewer electrical status epilepticus in sleep seizures and increased participation in everyday life. Professor Ulrich Brandl presented the case of **an 8-year-old boy with highly retarded mental development, SYNGAP1 mutation and aggressive behaviour**, who was experiencing 20–30 drop seizures/day despite treatment, and who required a wheelchair. After GW CBD initiation at 5 mg/kg/day, drop seizures were reduced by 30% and rapid improvements in his behaviour were observed; there were further reductions in drop seizures when

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the dose was increased to 10 mg/kg/day. Professor Selim Benbadis presented the case of a **26-year-old man with Lennox–Gastaut syndrome secondary to Down's syndrome**. Treatment with GW CBD was initiated at 5 mg/kg/day, which was increased to 10 mg/kg/day after 1 month, resulting in an 80% reduction in seizures and only a minor elevation of liver function test results, highlighting the benefit of optimal dosing for this patient.

Managing adverse events

Professor Sameer Zuberi presented the case of **a 15-year-old girl with SCN1A-positive Dravet syndrome**. GW CBD treatment was initiated at 2.5 mg/kg/day, which was increased to 5 mg/kg/day; the patient consequently experienced fewer atypical absence seizures and her communication improved. Faecal incontinence was experienced as a side effect of treatment, which was managed by reducing the dose of GW CBD from 10.2 mg/kg/day to 8.7 and then to 7.3 mg/kg/day, while maintaining the reduction in atypical seizures. Professor Bernhard Steinhoff presented the case of **a 28-year-old woman with Lennox–Gastaut syndrome refractory to most anti-epileptic drugs**. GW CBD add-on therapy was initiated with a target dose of 10 mg/kg/day. Weekly up-titration by 2 mg/kg/day was used, but led to sedation. The titration schedule was modified from weekly to fortnightly, which reduced the patient's sedation while resulting in a 30% decrease in seizure frequency. These cases highlight how GW CBD dose and schedule modifications can manage adverse events.

Determining the optimal dose of GW CBD

Professor Elizabeth Thiele presented the case of **a 16-year-old girl with Lennox–Gastaut syndrome refractory to treatment**. GW CBD add-on therapy was initiated and up-titrated to 20 mg/kg/day over a month, and the patient experienced a 50% reduction in seizure frequency. The GW CBD dose was reduced to 15 mg/kg/day, resulting in an 80% reduction in the patient's seizure frequency and improved alertness. Professor Steinhoff presented the case of **a 32-year-old man, who began treatment with add-on GW CBD 10 mg/kg/day, which resulted in a reduction in seizure frequency**. Up-titration of the GW CBD dose to 20 mg/kg/day resulted in an overall reduction in seizure frequency of 40%. These cases demonstrate how patients may benefit from a range of GW CBD doses, highlighting the need to optimise CBD dose individually for each patient, in collaboration with caregivers.

Management based on previous unregulated cannabidiol use

Professor Benbadis presented the case of **a 29-year-old woman with Lennox–Gastaut syndrome** who was receiving non-regulatory approved cannabis-based products of uncertain cannabidiol dosage from a dispensary, as well as other anti-epileptic drugs, but was continuing to experience seizures. She discontinued her non-regulatory approved cannabis-based products and treatment with GW CBD 5 mg/kg/day was initiated, which was up-titrated to 10 mg/kg/day resulting in a 90% reduction in seizures. This case highlights that the benefits offered by GW CBD may not be predicted by response to non-regulatory approved cannabis-based products as their cannabidiol concentration is often uncertain and may be lower than regulatory approved cannabis products.

Early intervention with GW CBD

The expert panel discussed the use of GW CBD as an intervention early in the disease course. The experts suggested that early intervention with GW CBD in patients with Dravet syndrome and Lennox–Gastaut syndrome may be likely to reduce seizure frequency and be well-tolerated due to its good safety profile, as it currently is when used as late intervention as discussed above. The potential for early intervention may be limited by the time taken to diagnose Dravet syndrome and Lennox–Gastaut syndrome.

These case studies highlight how to initiate treatment with GW CBD and find the optimal dose, how to manage adverse events and the challenges of unregulated cannabis products.

If you would like to hear more details on these case studies, please watch the full webinar, available here.

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Published: July 2021

Reference

1. European Medicines Agency. Epidyolex. Summary of product characteristics. Available at: **www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf** (accessed July 2021).

Date of preparation: July 2021
VV-MED-21766

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Great Britain Prescribing Information Epidyolex (cannabidiol) 100 mg/ml oral solution

(Please refer to the full Summary of Product Characteristics (SmPC) before prescribing)

PRESENTATION: One 100 ml bottle; each ml contains 100 mg cannabidiol

INDICATION: Use as adjunctive therapy of seizures associated with Lennox Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.
Posology / Method of Administration: Should be initiated and supervised by physicians with experience in the treatment of epilepsy.

DOSAGE: Oral solution. Should be taken consistently either with or without food. Recommended starting dose 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.

CONTRAINDICATIONS: Hypersensitivity to the active substance, to sesame oil, or to any of the excipients. Transaminase elevations greater than 3 times the upper limit of normal (ULN) and bilirubin greater than 2 times the ULN.

WARNINGS AND PRECAUTIONS: *Hepatocellular injury:* Cannabidiol causes dose related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). Prior to starting treatment with cannabidiol, obtain serum transaminases (ALT and AST) and total bilirubin levels. Routine Monitoring - transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment, and periodically thereafter or as clinically indicated. Upon changes in cannabidiol dose above 10 mg/kg/day or changes in medicinal products (dose change or additions) that are known to impact the liver, this monitoring schedule should be restarted. Intensified Monitoring - Patients with identified baseline elevations of ALT or AST and patients who are taking valproate should have serum transaminases and total bilirubin levels obtained at 2 weeks, 1 month, 2 months, 3 months, and 6 months after initiation of treatment with cannabidiol, and periodically thereafter or as clinically indicated. Upon changes in cannabidiol 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, transaminases and total bilirubin should be promptly measured and treatment should be interrupted or discontinued. Cannabidiol 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.
Somnolence and sedation: can cause somnolence and sedation, more commonly early in treatment and may diminish with continued treatment. The occurrence was higher for those patients on concomitant clobazam Other CNS depressants, including alcohol, can potentiate the somnolence and sedation effect.
Increased seizure frequency: As with other AEDs, a clinically relevant increase in seizure frequency may occur during treatment with cannabidiol, which may require adjustment in dose of cannabidiol and/or concomitant AEDs, or discontinuation of cannabidiol.
Suicidal behaviour and ideation: Patients should be monitored for signs of suicidal behaviour and ideation and appropriate treatment should be considered.
Ethanol in the formulation: Each ml of Epidyolex contains 79 mg of ethanol. Effects of alcohol in children less than 6 years old may include sleepiness, behavioural changes, and impaired ability to concentrate and participate in school activities. The alcohol content should be taken into account in pregnancy and high risk groups such as patients with liver disease.

DRUG INTERACTIONS: *CYP3A4 or CYP2C19 inducers*: Strong inducers of CYP3A4, such as carbamazepine, enzalutamide, mitotane, St. John's wort, and/or strong inducers of CYP2C19, such as rifampin, may decrease plasma concentrations of cannabidiol and decrease the effectiveness of cannabidiol. Dose adjustment may be necessary.
UGT inhibitors: Cannabidiol is a substrate for UGT1A7, UGT1A9 and UGT2B7. No formal drug-drug interaction studies have been conducted with cannabidiol in combination with UGT inhibitors.
Concomitant AED treatments: The pharmacokinetics of cannabidiol are complex and may cause interactions with concomitant AED treatments. Cannabidiol and/or concomitant AED treatment should therefore be adjusted during regular medical supervision and the patient should be closely monitored for adverse drug reactions. Monitoring of plasma concentrations should be considered.
Clobazam: When co administered, bi directional PK interactions occur. Based on a healthy volunteer study, elevated levels (3- to 4 fold) of N desmethylclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition. In addition, there was an increased exposure to 7 hydroxy cannabidiol (7 OH CBD; an active metabolite of cannabidiol), for which plasma area under the curve (AUC) increased by 47%. Increased systemic levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions. Concomitant use of cannabidiol and clobazam increases the incidence of somnolence and sedation compared with placebo. Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co administered with cannabidiol.

Valproate: Concomitant use increases the incidence of transaminase enzyme elevations. If clinically significant increases of transaminases occur, cannabidiol and/or concomitant valproate should be reduced or discontinued in all patients until a recovery of transaminase elevations are observed. Concomitant use of cannabidiol and valproate increases the incidence of diarrhoea and events of decreased appetite.
Stiripentol: When cannabidiol was combined with stiripentol there was an increase in stiripentol levels. Patients should be closely monitored for adverse drug reactions.
Phenytoin: Exposure to phenytoin may be increased when it is co-administered with cannabidiol, as phenytoin is largely metabolised via CYP2C9, which is inhibited by cannabidiol in vitro. Phenytoin has a narrow therapeutic index, so combining cannabidiol with phenytoin should be initiated with caution and if tolerability issues arise, dose reduction of phenytoin should be considered.
Lamotrigine: Lamotrigine is a substrate for UGT enzymes including UGT2B7 which is inhibited by cannabidiol in vitro. Lamotrigine levels may be elevated when it is co-administered with cannabidiol.
Potential for cannabidiol to affect other medicinal products: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9, and UGT2B7 Substrates - In vitro and in vivo (for caffeine) data predict drug drug interactions with CYP1A2 substrates (e.g., theophylline, caffeine), CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5' diphospho glucuronosyltransferase 1A9 (UGT1A9) (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 (e.g., gemfibrozil, morphine, lorazepam) when co administered with cannabidiol. Co administration of cannabidiol is also predicted to cause clinically significant interactions with CYP2C8 (repaglinide) and CYP2C9 (e.g., warfarin) substrates. In vitro data have demonstrated that cannabidiol inhibits CYP2C19, which may cause increased plasma concentrations of medicines that are metabolised by this isoenzyme such as clobazam and omeprazole. Dose reduction should be considered for concomitant medicinal products that are sensitive CYP2C19 substrates or that have a narrow therapeutic index. Because of potential inhibition of enzyme activity, dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, and CYP2C9 should be considered, if adverse reactions are experienced when administered concomitantly with cannabidiol. Because of potential for both induction and inhibition of enzyme activity, dose adjustment of substrates of CYP1A2 and CYP2B6 should be considered. *In vitro assessment of interaction with UGT enzymes - In vitro* data suggest that cannabidiol is a reversible inhibitor of UGT1A9 and UGT2B7 mediated activity at clinically relevant concentrations. The metabolite 7 carboxy cannabidiol (7 COOH CBD) is also an inhibitor of UGT1A1, UGT1A4 and UGT1A6 mediated activity in vitro. Dose reduction of the substrates may be necessary when cannabidiol is administered concomitantly with substrates of these UGTs.

PREGNANCY AND LACTATION: *Pregnancy*: should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus. Breast feeding: breast-feeding should be discontinued during treatment.

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES: Patients should be advised not to drive or operate machinery until they have gained sufficient experience to gauge whether it adversely affects their abilities.

UNDESIRABLE EFFECTS: *Very common*: Decreased appetite, somnolence, sedation, diarrhoea, vomiting, pyrexia, fatigue. *Common*: Pneumonia, bronchitis, nasopharyngitis, urinary tract infection, increased appetite, irritability, insomnia, aggression, abnormal behaviour, agitation, lethargy, drooling, tremor, cough, AST increased, ALT increased, GGT increased, liver function test abnormal, rash, weight decreased. *Other effects of note*: decreases in haemoglobin and haematrocrit, elevations in serum creatinine. (Please refer to the full SmPC for further information on side effects).

UK LIST PRICE: 100ml bottle £850.29
LEGAL CATEGORY: POM
MARKETING AUTHORISATION NUMBER: EU/1/19/1389/001
MARKETING AUTHORISATION HOLDER: GW Pharma (International) B,V., Databankweg26 3821 AL Amersfoort, The Netherlands.
FOR MORE INFORMATION PLEASE CONTACT: medinfo@gwpharm.com
DATE OF PREPARATION: August 2020 VV-MED-13079

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk, or search for MHRA Yellow Card in the Google Play or Apple App Store

Adverse events should also be reported to GW Pharma on medinfo@gwpharm.com

International Prescribing Information Epidyolex (cannabidiol) 100 mg/ml oral solution

(Please refer to the full Summary of Product Characteristics (SmPC) before prescribing)

PRESENTATION: One 100 ml bottle; each ml contains 100 mg cannabidiol

INDICATIONS: Use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS)or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.
Use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2years of age and older.
Posology / Method of Administration: Should be initiated and supervised by physicians withexperience in the treatment of epilepsy.

DOSAGE: Oral solution. Should be taken consistently either with or without food. When taken withfood, a similar composition of food should be considered, if possible.

	LGS and DS	**TSC**
Starting dose – first week	2.5mg/kg taken twice daily (5mg/kg/day)	
Second week	Maintenance dose 5mg/kg twice daily(10mg/kg/day)	5mg/kg twice daily(10mg/kg/day)
Further titration as applicable (incremental steps)	Weekly increments of 2.5mg/kg administered twice daily (5mg/kg/day)	
Maximal recommended dose	10mg/kg twice daily (20mg/kg/day)	12.5mg/kg twice daily (25mg/kg/day)

Any dose increases above 10mg/kg/day, up to the maximum recommended dose should be madeconsidering individual benefit and risk, and with adherence to the full monitoring schedule.

CONTRAINDICATIONS: Hypersensitivity to the active substance, or to any of the excipients. Transaminase elevations greater than 3 times the upper limit of normal (ULN) and bilirubin greaterthan 2 times the ULN.

WARNINGS AND PRECAUTIONS: *Hepatocellular injury*: Cannabidiol can cause dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase[AST]). Prior to starting treatment with cannabidiol, obtain serum transaminases (ALT and AST) and total bilirubin levels. Routine Monitoring - transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment, and periodically thereafter or as clinically indicated. Upon changes in cannabidiol dose above 10 mg/kg/day or changes in medicinal products (dose change or additions) that are known to impact the liver, this monitoring schedule should be restarted. Intensified Monitoring - Patients with identified baseline elevations of ALT or AST and patients who are taking valproate should have serum transaminases and total bilirubin levels obtained at 2 weeks, 1 month, 2 months, 3 months, and 6 months after initiation of treatment with cannabidiol, and periodically thereafter or as clinically indicated. Upon changes in cannabidiol 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, transaminases and total bilirubin should be promptly measured and treatment should be interrupted or discontinued.
Cannabidiol 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 possiblecauses.
Somnolence and sedation: Can cause somnolence and sedation, more commonly early in treatmentand may diminish with continued treatment. The occurrence was higher for those patients on concomitant clobazam. Other CNS depressants, including alcohol, can potentiate the somnolence and sedation effect.
Increased seizure frequency: As with other AEDs, a clinically relevant increase in seizure frequency may occur during treatment with cannabidiol, which may require adjustment in dose of cannabidioland/or concomitant AEDs, or discontinuation of cannabidiol.
Suicidal behaviour and ideation: Patients should be monitored for signs of suicidal behaviour andideation and appropriate treatment should be considered.
Decreased weight: Can cause weight loss or decreased weight gain which appeared to be dose- related. Decreased appetite and weight loss may result in slightly reduced height gain. Continuousweight loss/absence of weight gain should be periodically checked to evaluate if cannabidiol treatment should be discontinued.
Sesame oil in the formulation: Contains refined sesame oil which may rarely cause severe allergicreactions.
Benzyl alcohol: Contains 0.0003mg benzyl alcohol which may cause allergic reactions.
Populations not studied: Patients with clinically significant cardiovascular impairment were notincluded in the TSC clinical development programme.

DRUG INTERACTIONS: *CYP3A4 or CYP2C19 inducers*: Strong inducers of CYP3A4, such as carbamazepine, enzalutamide, mitotane, St. John's wort, and/or strong inducers of CYP2C19, such asrifampin, may decrease plasma concentrations of cannabidiol and decrease the effectiveness of cannabidiol. Dose adjustment may be necessary.

UGT inhibitors: Cannabidiol is a substrate for UGT1A7, UGT1A9 and UGT2B7. No formal drug-druginteraction studies have been conducted with cannabidiol in combination with UGT inhibitors.
Concomitant AED treatments: The pharmacokinetics of cannabidiol are complex and may cause interactions with concomitant AED treatments. Cannabidiol and/or concomitant AED treatment should therefore be adjusted during regular medical supervision and the patient should be closely monitored for adverse drug reactions. Monitoring of plasma concentrations should be considered.
Clobazam: When co-administered, bi-directional PK interactions occur. Based on a healthy volunteerstudy, elevated levels (3- to 4-fold) of N-desmethylclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition, with no effect on clobazam levels. In addition, there was an increased exposure to 7-hydroxy-cannabidiol (7-OH-CBD; an active metabolite of cannabidiol), for which plasma area under the curve (AUC) increased by 47%.Increased systemic levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions. Concomitant use of cannabidiol and clobazam increases the incidence of somnolence and sedation compared with placebo. Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co-administered with cannabidiol.
Valproate: Concomitant use increases the incidence of transaminase enzyme elevations. If clinicallysignificant increases of transaminases occur, cannabidiol and/or concomitant valproate should be reduced or discontinued in all patients until a recovery of transaminase elevations are observed.
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Stiripentol: When cannabidiol was combined with stiripentol there was an increase in stiripentollevels. Patients should be closely monitored for adverse drug reactions.
Phenytoin: Exposure to phenytoin may be increased when it is co-administered with cannabidiol, as phenytoin is largely metabolised via CYP2C9, which is inhibited by cannabidiol *in vitro*. Phenytoin hasa narrow therapeutic index, so combining cannabidiol with phenytoin should be initiated with caution and if tolerability issues arise, dose reduction of phenytoin should be considered.
Lamotrigine: Lamotrigine is a substrate for UGT enzymes including UGT2B7 which is inhibited by cannabidiol *in vitro*. Lamotrigine levels may be elevated when it is co-administered with cannabidiol.
Mammalian target of rapamycin (mTOR) or calcineurin inhibitors: No dedicated DDI studies have been conducted with mTOR inhibitors (eg. everolimus) or calcineurin inhibitors (eg. tacrolimus). Potential interaction may lead to increased plasma concentration of mTOR inhibitors/calcineurin inhibitors – co-administer with caution, and monitoring of mTOR/calcineurin inhibitor blood level should be considered.
Potential for cannabidiol to affect other medicinal products: *CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9, and UGT2B7 Substrates - In vitro* and *in vivo* (for caffeine) data predict drug-drug interactions with CYP1A2 substrates (e.g., theophylline, caffeine), CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5' diphospho-glucuronosyltransferase 1A9 (UGT1A9) (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 (e.g., gemfibrozil, morphine, lorazepam) when co-administered with cannabidiol. Co-administration of cannabidiol is also predicted to cause clinically significant interactions with CYP2C8 (repaglinide) and CYP2C9 (e.g., warfarin) substrates. *In vitro* data have demonstrated that cannabidiol inhibits CYP2C19, which may cause increased plasma concentrations of medicines that are metabolised by this isoenzyme such as clobazam and omeprazole. Dose reduction should be considered for concomitant medicinal products that are sensitive CYP2C19 substrates or that have a narrow therapeutic index. Because of potential inhibition of enzyme activity, dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, and CYP2C9 should be considered, if adverse reactions are experienced when administered concomitantly with cannabidiol.Because of potential for both induction and inhibition of enzyme activity, dose adjustment of substrates of CYP1A2 and CYP2B6 should be considered. *In vitro assessment of interaction with UGT enzymes - In vitro* data suggest that cannabidiol is a reversible inhibitor of UGT1A9 and UGT2B7-mediated activity at clinically relevant concentrations. The metabolite 7-carboxy-cannabidiol (7-COOH-CBD) is also an inhibitor of UGT1A1, UGT1A4 and UGT1A6-mediatedactivity *in vitro*. Dose reduction of the substrates may be necessary when cannabidiol is administered concomitantly with substrates of these UGTs.
Ethanol in the formulation: Each ml contains 79mg of ethanol, equivalent to 10% v/v anhydrousethanol. For an adult weighing 70kg, receiving the maximal single dose (12.5mg/kg), this is equivalent to 17ml of beer, of 7ml of wine per dose.

PREGNANCY AND LACTATION: *Pregnancy*: Should not be used during pregnancy unless the potentialbenefit to the mother clearly outweighs the potential risk to the foetus. *Breast-feeding*: Breast- feeding should be discontinued during treatment.

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES: Patients should be advised not to drive or operate machinery until they have gained sufficient experience to gauge whether it adversely affectstheir abilities.

UNDESIRABLE EFFECTS: *Very common*: Decreased appetite, somnolence, sedation, diarrhoea, vomiting, pyrexia, fatigue. *Common*: Pneumonia, urinary tract infection, irritability, aggression, lethargy, seizure, cough, nausea, AST increased, ALT increased, GGT increased, rash, weight decreased. *Other effects of note*: Decreases in haemoglobin and haematrocrit, elevations in serumcreatinine. (Please refer to the full SmPC for further information on side effects).

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FOR MORE INFORMATION PLEASE CONTACT: medinfo@gwpharm.com
DATE OF PREPARATION: April 2021 VV-MED-19823

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