SHARING EXPERIENCE WITH CANNABIDIOL (EPIDYOLEX®) 'GW CBD'

Highlights of a GW Pharmaceuticals-sponsored Epilepsy Focus webinar held on 2 July 2020

Cannabidiol (Epidyolex®) '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] 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.

Patient profiles

Professor Elizabeth Thiele presented the case of **a 5-year old boy with Dravet syndrome**, who started demonstrating fever-associated tonic-clonic seizures at 4 months of age. Despite treatment, seizure activity continued to worsen with age. At 4.5 years of age he was experiencing 1–2 tonic-clonic seizures per month so GW CBD was added to clobazam, stiripentol and a ketogenic diet. Following 1 year of GW CBD (15 mg/kg/day), he experienced two generalized tonic-clonic seizures both in the setting of febrile illness and no atypical absence seizures. He has also made significant developmental progress and his behavioural difficulties have been reduced. Professor Bernhard Steinhoff presented the case of **a 22-year old man with a history of retarded development in early childhood and tonic seizures**. Following confirmation of SCN1A-positive Dravet syndrome, GW CBD was added to his existing treatment regimen of valproic acid, perampanel and clobazam. This reduced the number of tonic seizures experienced by 50%, with no clear effect on cognition or behaviour.

Initiating and maintaining patients on GW CBD

Professor Angela Kaindl presented the case of **a 13-year old girl with Lennox–Gastaut syndrome**. Despite treatment she was experiencing 5–10 atypical absence seizures an hour and 5–6 tonic/atonic seizures a day. Treatment with 2 mg/kg/day GW CBD add-on therapy was initiated, and the dose was increased incrementally each week to 4, 8, 11 and 15 mg/kg/day, which was maintained. During the 3 months of GW CBD treatment, she experienced one tonic seizure every second day, and her sleep quality, speech production, and engagement with everyday life all improved. Professor Selim Benbadis presented the

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case of **a 15-year-old girl with static encephalopathy, developmental delay, intellectual disability, cerebral palsy and an electroencephalogram profile suggesting Lennox–Gastaut syndrome**. GW CBD was added to her existing clobazam regimen and was initiated at 5 mg/kg/day, which was increased to a maintenance dose of 10 mg/kg/day after 2 months. The patient experienced a significant reduction in tonic-clonic 'drop' seizures.

Managing adverse events

Professor Thiele presented a second case of **a 10-year-old boy with Dravet syndrome**, which was treatment refractory, who had retarded language and motor skills. Seizure frequency was reduced when GW CBD was added to stiripentol and clobazam; however, GW CBD treatment had to be subsequently tapered-off as the patient experienced diarrhoea from an allergy to the sesame seed oil used as an excipient in the GW CBD formulation. Professor Andreas Schulze-Bonhage presented the case of **a 30-year-old man with Lennox–Gastaut-like syndrome** initiated on GW CBD. He developed concentration difficulties and double vision due to a CYP1A2 mutation, which slowed the metabolism of GW CBD and valproic acid leading to high serum concentrations of these drugs. Consequently, treatment with GW CBD was halted. Overall, Professors Thiele and Schulze-Bonhage suggested that GW CBD has a good tolerability profile, with the main adverse effect being diarrhoea. There is the potential for drug–drug interactions, particularly with clobazam, but this can be managed by clobazam dose down-titration.

Management based on previous unregulated GW CBD use

Professor Ulrich Brandl discussed patients switching from unregulated cannabis products to GW CBD. Unregulated cannabis products have inconsistent purity and concentrations of active constituents, which may result in variable efficacy and adverse-event profiles. Consequently, a previous lack of efficacy with unregulated cannabis products is generally not indicative of potential benefit from GW CBD, which is dosed specifically according to weight. This point was demonstrated in a case study presented by Professor Benbadis of **a 42-year-old man with generalised convulsions and weekly episodes of stiffening**. He was taking a dispensary cannabis product, although receiving <10 mg/day of the active ingredient. When he was initiated on GW CBD which was up-titrated over 6 months to 10 mg/kg/day, a 70% reduction in clonic seizures was observed.

In summary, these case studies highlight the diverse range of patients who can be treated with GW CBD, how to up-titrate and adjust dosing to reduce the frequency of AEs and manage patents with previous experience 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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Reference

1. European Medicines Agency. Epidyolex. Summary of product characteristics.2019. Available at: www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf (accessed 27 August 2020).

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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.
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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