TOX/2020/02

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

CBD Update

Background and Introduction

Food

1. The potential medical applications of Cannabidiol (CBD) have been investigated and researched for several years, including its use in clinical trials for treatment of epilepsy and seizures. However, non-medicinal CBD-containing products are becoming increasingly popular and have now entered the food sector, including beverages (beer, spirits, wine, coffee and soda style drinks), oils (tinctures, drops, syrup, olive oils) chewables (gum drops) and chocolate. These products are classified as novel foods which means there is no significant history of consumption in the EU and they need to be authorised before being placed on the market.

Cosmetics

2. There are a number of CBD products on the market in the cosmetic sector for topical use. These include but are not limited to serums, creams, washes/rinse-off products (cleansers, shampoos, conditioners, body washes, masks), bath products (capsules, oils, tablets and salts), deodorants, balms and toothpastes. CBD-containing cosmetic products do not require pre-market authorisation. These products may contribute to CBD exposure via dermal absorption[1].

3. However, as the aim of this paper is to provide the COT with an update of the medicinal data (clinical trials) which was requested at the discussion in the July 2019 COT meeting and to consider possible risk assessment options, the non-oral routes of CBD exposure will not be considered in the rest of this paper. However, Members will want to be aware that it is likely that a COT paper on CBD dermal exposure will be presented in due course.

Previous COT discussions

4. Risk assessment advice on CBD has been increasingly requested from the Food Standards Agency (FSA). It was therefore considered timely for the available toxicological information on CBD to be reviewed.

[1] Some medicinal examples using a dermal route include:

Giacoppo, S., Galuppo, M., Pollastro, F., Grassi, G., Bramanti, P. and Mazzon, E., 2015. A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. DARU Journal of pharmaceutical sciences, 23(1), p.48.

Hammell, D.C., Zhang, L.P., Ma, F., Abshire, S.M., McIlwrath, S.L., Stinchcomb, A.L. and Westlund, K.N., 2016. Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. European journal of pain, 20(6), pp.936-948.

5. In July 2019, a scoping paper on the potential adverse effects of CBD products (TOX/2019/32[2]) was presented to the Committee on Toxicity of Chemicals in Food, Consumer Products and The Environment (COT).

6. The Committee noted that some CBD products would not only contain CBD but also a range of other cannabinoids including tetrahydrocannabinol (THC), potentially due to different extraction/manufacturing methods. It was noted that the presence of THC above certain levels would mean that the product would not be authorised as a novel food and would become the responsibility of the Home Office under legislation on the mis-use of drugs.

7. The Committee agreed that there was potential for interactions between the cannabinoids present in CBD products and this in turn, could affect the potential adverse effects of CBD.

8. It was highlighted that based on the currently available *in vitro* and *in vivo* data, CBD appeared to have the following adverse effects: hepatoxicity, immunotoxicity, reproductive toxicity, changes to organ weights and alterations to drug metabolizing enzymes (P450), suggesting adverse effects could occur in consumers. The changes to drug metabolizing enzymes following CBD exposure indicated the potential for drug interactions.

9. The Committee agreed that there was a lack of toxicological information especially in the areas of reproduction and immunology. The information was of limited quality and it was unclear to what extent it was applicable to the CBD products currently on the market given their heterogeneity.

10. The COT concluded that it could not reach a conclusion on the safety in use of CBD products based on the information presented[3]. The Committee agreed this topic should be reviewed once more data became available. It was agreed that the data from the medicinal/pharmaceutical sector would be very useful if it could be obtained as most of it was currently not publicly available. However, it was important to note that the safety profile of CBD food grade might be different to that of medical grade products due to differences in composition.

11. As the genotoxicity data were conflicting but indicated genotoxic potential in some but not all *in vivo* studies, the Committee recommended the genotoxicity data be referred to Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) for consideration. The COM concluded that the *in vitro* and *in vivo* genotoxicity studies were inadequate and therefore a conclusion on the genotoxic potential could not be reached.

Newly available data on Epidiolex®

12. Thanks to cooperation from GW Pharmaceuticals[4] (the manufacturers of Epdiolex®), the Secretariat were able to examine and discuss recent clinical and non-clinical data on the medicinal form of CBD which is now publicly available online

[2] https://cot.food.gov.uk/sites/default/files/tox2019-32.pdf
[3] https://cot.food.gov.uk/sites/default/files/cotdraftminutesjuly2019finalamended.pdf
[4] https://www.gwpharm.co.uk/

(ANNEX A). This paper will provide an overview of the data used by the United States (U.S.) Food and Drug Administration (FDA) to evaluate and approve (June 2018[5]) the first oral solution drug (Epidiolex®) and The European Medicines Agency (EMA) Assessment report (2019) as well as the scientific submission of GW Pharmaceuticals highlighting some of the key adverse reactions and considering the possibilities of undertaking a provisional risk assessment using the Lowest Observed Adverse Effect Level (LOAEL) approach.

13. When considering the data on medicinal products, it should be noted that there will be trade-off between risks and benefits that does not apply to food.

Epidiolex® Data

14. Epidiolex® is a prescription medicine[6] that is used to treat seizures associated with Lennox-Gastaut syndrome (LGS) [7]or Dravet syndrome[8] in patients 2 years of age and older. Symptoms include multiple types of seizure (fits), abnormal electrical activity in the brain, learning disability and behavioural problems. These conditions are rare, and Epidiolex was designated an 'orphan medicine[9]'.

15. The information presented is scientific data from non-clinical trials and clinical trials for the Epidiolex® medicine approval package. Some of the data that is publicly available data is in a redacted form. Only the publicly available information has been used in this paper.

Product Formulation

16. The medicinal substance is produced from an extract of *Cannabis sativa L*. plants (*i.e.* botanical substance CBD > 98% purity). The medicinal product is a 100 mg/mL, non-sterile, non-preserved, non-aqueous oral solution of CBD dissolved in sesame oil, flavouring agent strawberry flavour, sucralose and dehydrated alcohol. The medicinal product is packaged in a 105 mL amber glass bottle. It contains no ingredients made from a gluten-containing grain (wheat, barley, or rye)[10].

Ethanol in the formulation

17. Each ml of Epidiolex® contains 79 mg of ethanol. The maximum recommended single dose of Epidiolex® (10 mg/kg) will increase the concentration of ethanol in the body by about 13 mg/l. For an adult weighing 70 kg, this is equivalent to 14 millilitres (ml) of beer, or 6 ml of wine per dose.

[5] https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms
[6] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[7] Lennox–Gastaut syndrome (LGS): a complex, rare, and severe childhood-onset epilepsy.
[8] Dravet syndrome, previously known as severe myoclonic epilepsy of infancy (SMEI), is a type of epilepsy with seizures that are often triggered by hot temperatures or fever.
[9]Orphan medicine: a medicine used in rare diseases.
[10] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

Overview of Pharmacokinetic (PK) data

Parameter		Reference
Solubility	Insoluble in water	FDA[11]
Purity	>98%	EMA[12]
T_{max}	2.5 to 5 hours at steady state Steady state T_{max} of CBD is approximately 3 hours	EMA[13]
C_{max}	332 ng/mL 750mg (10mg/kg)	FDA[14]
Protein Binding	> 94% protein bound	FDA[15]
Mechanism of action	Reduces neuronal hyperexcitability and inflammation through modulation of intracellular calcium via GPR55 and TRPV1 channels and modulation of adenosine-mediated signalling.	FDA[16]
AUC ng/ h/mL	The representative clinical plasma CBD exposure (AUC 0-24) for comparison with toxicokinetic data from the toxicity studies is approximately 2800 ng h/mL	FDA[17]
T ½	Estimated from 51-202 hours	EMA[18]
Food effect	Significant food effect was observed in the conducted fed study and both C_{max} and AUC was 4-5-times increased following administration of study drug with standard high fat meal. T_{max} was not significantly affected by administration with food	EMA[19]
Bioavailability	6.5 %	FDA[20]
Bioavailability	Following administration of food: 14-25%	FDA[21]
Distribution	The apparent volume of distribution in healthy volunteers was 20963 L to 42849 L. Protein binding of the CBD and its metabolites was >94% *in vitro*.	FDA[22]
Metabolism	CBD is metabolized in the liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms After repeat dosing, the active metabolite of CBD, 7-OH-CBD, has a 38% lower AUC than the parent drug. The 7-OH-CBD metabolite is converted to 7-COOH-CBD, which has an approximately 40-fold higher AUC than the parent drug. Based on preclinical models of seizure, the 7-OH-CBD metabolite is active; however, the 7-COOH-CBD metabolite is not active.	FDA[23]
Metabolism	CBD is extensively metabolised by the liver via CYP450 enzymes and the UGT enzymes. The major CYP450 isoforms responsible for the phase I metabolism of CBD are CYP2C19 and CYP3A4. The UGT isoforms responsible for the phase II conjugation of CBD are UGT1A7, UGT1A9 and UGT2B7.	EMA[24]

[11] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[12] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[13] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[14] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[15] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[16] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[17] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[18] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[19] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[20] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[21] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[22] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[23] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[24] https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf

	Studies in healthy subjects showed there were no major differences in the plasma exposure to CBD in CYP2C19 intermediate and ultra-rapid metabolisers when compared to extensive metabolisers. The phase I metabolites identified in standard *in vitro* assays were 7-COOH-CBD, 7-OH-CBD, and 6-OH-CBD (a minor circulating metabolite). After multiple dosing with CBD, the 7-OH-CBD metabolite (active in a preclinical model of seizure) circulates in human plasma at lower concentrations than the parent drug CBD (~ 40% of CBD exposure) based on AUC.	
Elimination	The half-life of CBD in plasma was 56 to 61 hours after twice-daily dosing for 7 days in healthy volunteers. The plasma clearance of CBD following a single Epidiolex® 1500 mg dose (1.1 times-The maximum recommended daily dosage) is 1111 L/h.	FDA[25]
Excretion	16% of total dose was excreted in urine within 72 hours, indicating that renal excretion is a minor route of excretion for CBD. A large proportion of CBD was excreted unchanged in faeces. In humans, hepatic clearance is a major route of CBD metabolism. The mean CL/F of CBD in healthy subjects ranged between 375 and 1909 L/h (fasted after a single dose of between 200-6000 mg) Following a single oral dose of 14C-CBD at 5mg/kg, radioactivity was excreted predominantly via the faecal route (84 %) and smaller proportions of administered radioactivity recovered in the urine (8%). The total recover after 168 hours was 94%.	EMA[26]

Main Adverse Reactions

18. The Epidiolex® development program indicates that[27]:

- Side effects of CBD emerge at all doses studied in clinical trials in humans.
- Liver toxicity manifests at the lowest dose for which it has been systematically monitored and may occur at even lower doses.
- Drug-drug interactions are apparent at low doses.
- Miscellaneous variables can affect the body's exposure to CBD's risks, for example, whether CBD is taken with food, as well as the composition of such food. When taken with a high fat meal, for instance, the body is exposed to up to 500% more CBD than if taken while fasting[28].

[25] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[26] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[27] https://www.regulations.gov/document?D=FDA-2019-N-1482-4257
[28] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000ClinPharmR.pdf

19. In the EMA Assessment report[29] it states the following treatment emergent adverse events (TEAS) under Phase II and Phase II controlled clinical trials:

- There were more TEAS in the CBD Oral Solution (CBD-OS) treated groups than in the placebo groups.
- There were more TEAS in the 20 mg/kg/day than the 10 mg/kg/day CBD-OS groups.
- The TEAS in the DS and LGS pools were similar except for a few SOCs mentioned below.

20. Most commonly reported adverse events were within:
- The system organ class (SOC) 'Nervous system disorders', including somnolence, lethargy, sedation, drooling and tremor.
- The SOC 'Gastrointestinal disorders', including diarrhoea, vomiting.
- The SOC 'Metabolism', including decreased appetite.
- The SOC 'Investigations', including changes in the levels of hepatic enzymes.

21. In the CBD-OS treated LGS group four subjects had recorded cardiac disorders of tachycardia (II), arrhythmia (I) and bradycardia (I) as compared to one subject in the placebo group. As no CBD-OS treated subjects with DS had similar changes of rhythm, and as the reported incidence/prevalence is fairly comparable to the background prevalence, it is less likely to be related to CBD.

22. The most frequently reported AEs during controlled DS and LGS trials are summarised in Table 1 below:

[29] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf

Table 1. Incidence of common TEAEs (≥3% of patients in all CBD-OS group) in controlled DS and LGS trials (Pool DS/LGS)

SOC PT	CBD-OS 5 mg/kg/day (N=10) n (%)	CBD-OS 10 mg/kg/day (N=139) n (%)	CBD-OS 20 mg/kg/day (N=307) n (%)	All CBD-OS (N=456) n (%)	Placebo (N=292) n (%)
Patients with at least 1 TEAE	**8 (80.0)**	**117 (84.2)**	**277 (90.2)**	**402 (88.2)**	**222 (76.0)**
Gastrointestinal disorders	**1 (10.0)**	**30 (21.6)**	**118 (38.4)**	**149 (32.7)**	**73 (25.0)**
Diarrhoea	0	18 (12.9)	65 (21.2)	83 (18.2)	28 (9.6)
Vomiting	1 (10.0)	0 9 (6.5)	40 (13.0)	50 (11.0)	30 (10.3)
Constipation	1 (10.0)	5 (3.6)	12 (3.9)	18 (3.9)	12 (4.1)
General disorders and administration site conditions	**3 (30.0)**	**36 (25.9)**	**86 (28.0)**	**125 (27.4)**	**52 (17.8)**
Pyrexia	3 (30.0)	24 (17.3)	45 (14.7)	72 (15.8)	35 (12.0)
Fatigue	0	10 (7.2)	41 (13.4)	51 (11.2)	15 (5.1)
Infections and infestations	**4 (40.0)**	**59 (42.4)**	**130 (42.3)**	**193 (42.3)**	**96 (32.9)**
Upper respiratory tract infection	1 (10.0)	14 (10.1)	24 (7.8)	39 (8.6)	25 (8.6)
Nasopharyngitis	0	8 (5.8)	25 (8.1)	33 (7.2)	18 (6.2)
Pneumonia	0	10 (7.2)	12 (3.9)	22 (4.8)	2 (0.7)
Ear infection	0	5 (3.6)	8 (2.6)	13 (2.9)	7 (2.4)
Bronchitis	0	2 (1.4)	10 (3.3)	12 (2.6)	6 (2.1)
Sinusitis	0	4 (2.9)	8 (2.6)	12 (2.6)	7 (2.4)
Investigations	**2 (20.0)**	**29 (20.9)**	**85 (27.7)**	**116 (25.4)**	**42 (14.4)**
ALT increased	0	6 (4.3)	21 (6.8)	27 (5.9)	3 (1.0)
AST increased	0	5 (3.6)	20 (6.5)	25 (5.5)	2 (0.7)
Weight decreased	0	2 (1.4)	13 (4.2)	15 (3.3)	4 (1.4)
GGT increased	0	6 (4.3)	14 (4.6)	20 (4.4)	6 (2.1)
Liver function test abnormal	0	0	12 (3.9)	12 (2.6)	1 (0.3)
Metabolism and nutrition disorders	**1 (10.0)**	**27 (19.4)**	**84 (27.4)**	**112 (24.6)**	**28 (9.6)**
Decreased appetite	0	23 (16.5)	73 (23.8)	96 (21.1)	22 (7.5)
Increased appetite	0	4 (2.9)	8 (2.6)	12 (2.6)	3 (1.0)
Nervous system disorders	**6 (60.0)**	**59 (42.4)**	**151 (49.2)**	**216 (47.4)**	**97 (33.2)**
Somnolence	2 (20.0)	33 (23.7)	76 (24.8)	111 (24.3)	28 (9.6)
Convulsion	0	9 (6.5)	23 (7.5)	32 (7.0)	22 (7.5)
Status epilepticus	1 (10.0)	12 (8.6)	16 (5.2)	29 (6.4)	16 (5.5)
Lethargy	0	4 (2.9)	19 (6.2)	23 (5.0)	7 (2.4)
Sedation	2 (20.0)	3 (2.2)	16 (5.2)	21 (4.6)	2 (0.7)
Psychiatric disorders	**3 (30.0)**	**23 (16.5)**	**66 (21.5)**	**92 (20.2)**	**33 (11.3)**
Irritability	0	10 (7.2)	15 (4.9)	25 (5.5)	5 (1.7)
Aggression	0	3 (2.2)	15 (4.9)	18 (3.9)	3 (1.0)
Insomnia	0	5 (3.6)	10 (3.3)	15 (3.3)	6 (2.1)
Respiratory, thoracic and mediastinal disorders	**0**	**14 (10.1)**	**46 (15.0)**	**60 (13.2)**	**34 (11.6)**
Cough	0	6 (4.3)	13 (4.2)	19 (4.2)	9 (3.1)
Skin and subcutaneous tissue disorders	**1 (10.0)**	**18 (12.9)**	**35 (11.4)**	**54 (11.8)**	**18 (6.2)**
Rash[a]	0	3 (2.2)	16 (5.2)	19 (4.2)	3 (1.0)

a One additional patient in Pool DS (R-1187-004) randomized to 20 mg/kg/day CBD-OS had a non-serious TEAE of rash on Day 28 that resolved on Day 58 with no action taken regarding IMP. The event was of mild intensity and was not considered treatment-related by the investigator. The CRF AE page for this event was not provided to the sponsor until after database lock and was therefore not entered into the clinical database for this trial. Further details are provided in GWEP1424 CSR Section 5.6.4 and Section 9.3.1.4.3.

Note: Safety analysis set.

Source: ISS Table DSLGS.9.3.1.

CBD induces liver injury

23. It was stated in GW Pharmaceuticals Scientific Submission statement[30] that Epidiolex® was associated with dose-related increases in liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) including some elevations more than 5 times the upper limit of normal (ULN), which defines drug induced liver injury (DILI), and therefore causes liver injury[31]. These elevations appear to be due to a direct hepatocellular effect of CBD-OS or its metabolites. Although the mechanism is not fully understood, pathway-based investigations of the mechanism(s) responsible for this effect, including those involving mitochondrial function, are under way. Liver safety findings in humans are consistent with non-clinical toxicological data obtained during early Epidiolex® development, where the liver was the primary organ that was affected in two species (rats and dogs). Findings in two species included hepatocellular hypertrophy[32] accompanied by increases in ALT and ALP levels.

24. FDA's approved label for Epidiolex® recommends that physicians monitor patient liver function with blood tests[33]. This recommendation arises from the Epidiolex® clinical trials, where liver enzyme elevations were observed at a sub-therapeutic dose of 5 mg/kg/day. Of the 10 patients with Dravet syndrome who received CBD at 5 mg/kg/day for three weeks, one patient developed ALT >5X ULN, which meets DILI criteria. In a separate healthy volunteer Phase I study, 5 out of 12 healthy subjects developed ALT elevations above the normal range at 5 mg/kg/day during the three-week treatment period. In the same Phase I study, no liver transaminase elevations were observed at the lowest dosage of 1 mg/kg/day. Despite a limited number of subjects and the short treatment duration, it was stated that there was a clear signal for hepatotoxicity, including DILI, at a dosage of 5 mg/kg/day. However, below this dosage, systematic collection of data was lacking and the risk of hepatotoxicity unknown.

25. In controlled clinical trials, increasing exposure to CBD was closely correlated with an increased frequency of treatment emergent (TE) ALT elevations and DILI. The risk factors for ALT elevations include concomitant valproate[34] (VPA) use, ALT elevation at baseline, and CBD-OS dosage of 20 mg/kg/day or higher. The onset of ALT elevations occurred within the first 30 days of continuous treatment with CBD-OS but can appear later on, especially in patients taking concomitant VPA. Transaminase elevations resolved with discontinuation of, or reduction of CBD-OS or concomitant VPA in about two-thirds of the cases. In about one-third of the cases, transaminase elevations resolved during continued treatment with CBD-OS, without dose reduction.

26. Therefore, CBD has been demonstrated to cause hepatocellular injury.

27. The EMA report[35] also states that CBD causes dose-related elevations of ALT and AST. In controlled studies for LGS and DS, the incidence of ALT elevations

[30] https://www.regulations.gov/document?D=FDA-2019-N-1482-4257
[31] https://www.regulations.gov/document?D=FDA-2019-N-1482-4257
[32] Hepatocellular hypertrophy: morphological enlargement of hepatocytes.
[33] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[34] Valproate: medication primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches.
[35] https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf

above 3 times the ULN was 13% in CBD-treated patients compared with 1% in patients on placebo. Less than 1% of CBD-treated patients had ALT or AST levels greater than 20 times the ULN. There were also cases of transaminase elevations associated with hospitalisation in patients taking CBD. ALT elevations greater than 3 times the ULN were reported in 16% of patients taking CBD at as dose of 20 mg/kg/day compared with 3% in patients taking CBD at 10 mg/kg/day.

28. In controlled trials, in patients taking CBD 20 mg/kg/day, the frequency of treatment-emergent baseline transaminase elevations (ALT elevations) greater than 3 times the ULN was 31% (84% of these were patients were also taking valproate) when ALT was above the ULN at baseline, compared to 12% (89% of these were on valproate) when ALT was within the normal range at baseline. Five percent (5%) of patients (all on valproate) taking CBD at 10 mg/kg/day experienced ALT elevations greater than 3 times the ULN when ALT was above the ULN at baseline, compared with 3% of patients (all on valproate) in whom ALT was within the normal range at baseline.

Drug-drug interactions occur with CBD

29. In the GW Pharmaceuticals Submission of Scientific Data[36], it is stated that CBD drug-drug interactions (DDIs) may pose serious safety risks, depending on the underlying concurrent medication or substance. It is also stated that multiple scientific studies have demonstrated that CBD causes significant DDIs with other medications. The prescribing information for Epidiolex® describes and cautions on the known DDI with VPA and states that additional potential DDIs could result based on modulation of drug metabolizing enzymes by either CBD or other substrates.

30. GW Pharmaceuticals continues to study the DDI potential of Epidiolex® and it has been reported that case reports of DDIs continue to emerge. For instance, a case report (Grayson *et al*., 2018) observed a clinically significant interaction between Epidiolex® and warfarin[37] (7.5 mg), one of the most widely used oral anticoagulants, with a narrow therapeutic window. A patient with Marfan syndrome[38], mechanical mitral valve replacement[39], warfarin therapy, and post-stroke epilepsy was enrolled in a physician initiated expanded access program for the compassionate use of Epidiolex®. During titration of Epidiolex® (starting at 5 mg/kg/day and increasing in 5 mg/kg/day increments every two weeks), an increase in international normalized ratio (INR) (blood clotting) was noted. To maintain safe levels, the patient's warfarin dose was reduced by approximately 30 percent followed by an INR decrease to pre- Epidiolex® (Grayson *et al*., 2018). It was stated that it is critically important that patients using warfarin remain within a certain INR range.

31. The above case study showing a significant DDI with warfarin (a CYP2C19 substrate), coupled with the observation from GW Phase I DDI studies that CBD in healthy volunteers can cause potentially clinically significant CYP2C19 inhibition at doses as low as 1 mg/kg/day, strongly suggests that there is significant risk associated with co-administration of CBD at doses of 1 mg/kg (or lower to account

[36] https://www.regulations.gov/document?D=FDA-2019-N-1482-4257
[37] Warfarin, sold under the brand name Coumadin among others, is a medication that is used as an anticoagulant.
[38] Marfan syndrome (MFS) is a genetic disorder of the connective tissue.
[39] Mitral valve replacement is a procedure whereby the diseased mitral valve of a patient's heart is replaced by either a mechanical or tissue (bioprosthetic) valve.

for heterogenous population uncertainty factors) with narrow therapeutic margin drugs metabolised by CYP2C19 (*e.g.*, warfarin, clopidogrel[40], phenobarbital, tricyclic antidepressants).

32. In addition, in CBD treated patients, the incidence of ALT elevations greater than 3 times the ULN was 23% in patients taking both concomitant valproate and clobazam[41], 17% in patients taking concomitant valproate (without clobazam), 3% in patients taking concomitant clobazam (without valproate), and 2% in patients taking neither medicine.

33. The EMA Assessment report[42] also included a section assessing drug interactions in human volunteers, stating the following: Potential interactions between CBD (750 mg twice daily in healthy volunteers and 20 mg/kg/day in patients) and other AEDs were investigated in drug-drug interaction studies in healthy volunteers and in patients in a population pharmacokinetic analysis of plasma drug concentrations from placebo-controlled studies in the treatment of patients with LGS. The combination of CBD with clobazam caused an elevation in exposure to the active metabolite N desmethylclobazam. Although exposure to CBD was not notably affected by clobazam use, the levels of an active metabolite, 7-OH-CBD, were elevated by this combination.

34. The interactions are summarised in Table 2 below and the frequency of ALT elevations in patients with or without concomitant valproate in Table 3 and Table 4.

Table 2. Drug interactions between CBD and concomitant antiepileptic drugs

Concomitant AED	Influence of AED on cannabidiol	Influence of cannabidiol on AED
Clobazam	No effect on cannabidiol levels. Interaction resulting in an increase in exposure of the active metabolite 7-OH-CBD in HV* studies. [a]	No effect on clobazam levels. Interaction resulting in approximately 3-fold increase in N-desmethylclobazam metabolite exposure. [b]
Valproate	No effect	No effect
Stiripentol	No effect on cannabidiol levels. Interaction resulting in a decrease (approximately 30%) in C_{max} and AUC of the active metabolite 7-OH-CBD in HV* trials.	Interaction resulting in an approximate 28% increase in C_{max} and 55% increase in AUC.

[a] average increases of 47% in AUC and 73% in C_{max} [b] based on C_{max} and AUC
* HV=Healthy Volunteer

[40] Clopidogrel, sold under the trade name Plavix among others, is an antiplatelet medication used to reduce the risk of heart disease and stroke in those at high risk.
[41] Clobazam is used with other medication(s) to control seizures in adults and children.
[42] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf

Table 3. Frequency of ALT elevations by baseline ALT in patients with or without concomitant valproate in pool DS/LGS (Pivotal DS and LGS)

Peak ALT (× ULN)	No Concomitant Valproate Baseline ALT ≤ ULN	No Concomitant Valproate Baseline ALT > ULN	Concomitant Valproate Baseline ALT ≤ ULN	Concomitant Valproate Baseline ALT > ULN
	CBD-OS 20 mg/kg/day (N=106) *n / N* (%)	CBD-OS 20 mg/kg/day (N=38) *n / N* (%)	CBD-OS 20 mg/kg/day (N=129) *n / N* (%)	CBD-OS 20 mg/kg/day (N=25) *n / N* (%)
> 2 ×	5/106 (4.7)	8/35 (22.9)	45/129 (34.9)	18/23 (78.3)
> 3 ×	3/106 (2.8)	3/35 (8.6)	25/129 (19.4)	16/25 (64.0)
> 5 ×	3/106 (2.8)	0/38	8/129 (6.2)	9/25 (36.0)
> 8 ×	0/106	0/38	3/129 (2.3)	4/25 (16.0)
> 10 ×	0/106	0/38	1/129 (0.8)	3/25 (12.0)
> 20 ×	0/106	0/38	0/129	1/25 (4.0)
	CBD-OS 10 mg/kg/day (N=52) *n / N* (%)	CBD-OS 10 mg/kg/day (N=12) *n / N* (%)	CBD-OS 10 mg/kg/day (N=58) *n / N* (%)	CBD-OS 10 mg/kg/day (N=9) *n / N* (%)
> 2 ×	4/52 (7.7)	0/12	7/58 (12.1)	1/8 (12.5)
> 3 ×	1/52 (1.9)	0/12	3/58 (5.2)	1/9 (11.1)
> 5 ×	0/52	0/12	1/58 (1.7)	1/9 (11.1)
> 8 ×	0/52	0/12	1/58 (1.7)	0/9
> 10 ×	0/52	0/12	0/58	0/9
> 20 ×	0/52	0/12	0/58	0/9
	Placebo (N=108) *n / N* (%)	Placebo (N=32) *n / N* (%)	Placebo (N=123) *n / N* (%)	Placebo (N=22) *n / N* (%)
> 2 ×	2/108 (1.9)	3/28 (10.7)	3/123 (2.4)	4/19 (21.1)
> 3 ×	1/108 (0.9)	0/31	1/123 (0.8)	0/22
> 5 ×	1/108 (0.9)	0/32	1/123 (0.8)	0/22
> 8 ×	0/108	0/32	1/123 (0.8)	0/22
> 10 ×	0/108	0/32	1/123 (0.8)	0/22
> 20 ×	0/108	0/32	1/123 (0.8)	0/22

N corresponds to the total number of patients in the treatment group.
n / N: *n* = number of patients who had 1 or more elevations above the criterion any time post-baseline but not at baseline. *N* = number of patients who did not have an elevation above the criterion at baseline.

Table 4. Frequency of ALT elevation by baseline ALT in patients with or without concomitant valproate in pool LT-DS/LGS

Peak ALT (× ULN)	No Concomitant Valproate Baseline ALT ≤ ULN	No Concomitant Valproate Baseline ALT > ULN	Concomitant Valproate Baseline ALT ≤ ULN	Concomitant Valproate Baseline ALT > ULN
	CBD-OS (N=245) *n / N* (%)	CBD-OS (N=80) *n / N* (%)	CBD-OS (N=293) *n / N* (%)	CBD-OS (N=55) *n / N* (%)
> 2 ×	21/245 (8.6)	18/77 (23.4)	104/293 (35.5)	33/51 (64.7)
> 3 ×	9/245 (3.7)	9/78 (11.5)	63/293 (21.5)	25/55 (45.5)
> 5 ×	3/245 (1.2)	2/80 (2.5)	21/293 (7.2)	12/55 (21.8)
> 8 ×	0/245	2/80 (2.5)	9/293 (3.1)	5/55 (9.1)
> 10 ×	0/245	2/80 (2.5)	5/293 (1.7)	4/55 (7.3)
> 20 ×	0/245	1/80 (1.3)	0/293	1/55 (1.8)

N corresponds to the total number of patients in the treatment group.
n / N: *n* = number of patients who had 1 or more elevations above the criterion any time post-baseline but not at baseline. *N* = number of patients who did not have an elevation above the criterion at at baseline.

Other side effects and adverse reactions

35. In the GW Pharmaceuticals Scientific Submission statement[43], it also stated that CBD causes other common side effects that can pose safety risks. In patients with Dravet or LGS receiving ≥ 5 mg/kg/day up to 20 mg/kg/day Epidiolex®, the overall incidence of all causality adverse events (AEs) increased as the dose increased and exceeded placebo. The same dose-related incidence of all-causality AEs was seen in healthy subjects receiving either a single dose of Epidiolex® or multiple doses of Epidiolex®. The most common adverse reactions that occurred in patients (incidence at least 10% and greater than placebo) were: somnolence; decreased appetite; diarrhoea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor-quality sleep; and infections. The most common adverse reactions in Epidiolex®-treated patients (incidence at least 10% and greater than placebo) were somnolence; decreased appetite; diarrhoea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor-quality sleep; and infections.

36. For most of these adverse events, the incidence typically increased with increasing Epidiolex® dose. The incidence was similar in both Epidiolex® dose groups for the adverse events of somnolence (most commonly reported) and pyrexia[44]. Thus, even exposure at the lowest dose of Epidiolex® studied in Dravet patients resulted in adverse events that were also commonly observed with the higher doses.

37. Somnolence (sleepiness) was the most common AE across all groups in the double-blind clinical trials (randomized controlled trials (RCTs)) and was consistently more frequent in patients treated with Epidiolex® compared with placebo. Somnolence was the third most common treatment-emergent AE leading to discontinuation of Epidiolex®. The Epidiolex® label advises prescribers to monitor patients for somnolence and sedation and to advise patients not to drive or operate machinery until they have gained sufficient experience on Epidiolex®. It also stated that somnolence could be a serious issue if a consumer, who is unaware of this effect, ingested a CBD consumer product and then operated a vehicle or engaged in other potentially hazardous activities. Other central nervous system (CNS) depressants, including alcohol, could magnify the somnolence and sedation effect of CBD[45].

38. Additionally, gastrointestinal (GI) disorder-related AEs were frequently reported (Table 5). The most common AEs within the GI disorders were diarrhoea, vomiting, nausea and constipation. The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

[43] https://www.regulations.gov/document?D=FDA-2019-N-1482-4257
[44] Pyrexia: raised body temperature; fever.
[45] https://www.regulations.gov/document?D=FDA-2019-N-1482-4257

Table 5. Tabulated list of adverse reactions (EMA Assessment Report)[46]

System Organ Class	Frequency	Adverse reactions from clinical trials
Infections and infestations	Common	Pneumonia[a], bronchitis, nasopharyngitis, urinary tract infection
Metabolism and nutrition disorders	Very common	Decreased appetite
Metabolism and nutrition disorders	Common	Increased appetite
Psychiatric disorders	Common	Irritability, insomnia, aggression, abnormal behaviour, agitation
Nervous system disorders	Very common	Somnolence[a]
Nervous system disorders	Common	Lethargy, drooling, tremor
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very common	Diarrhoea, vomiting
Hepatobiliary disorders	Common	AST increased, ALT increased, Gamma glutamyltransferase (GGT) increased, liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Rash
General disorders and administration site conditions	Very common	Pyrexia, fatigue
Investigations	Common	Weight decreased

[a] Grouped Terms: **Pneumonia**: Pneumonia, Pneumonia RSV, Pneumonia mycoplasmal, Pneumonia adenoviral, Pneumonia viral, Aspiration pneumonia; **Somnolence:** Somnolence, Sedation.

[46] https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf

Table 6. Adverse reactions in patients treated with Epidiolex® in controlled trials in percentage/ numbers format.

Adverse Reactions	EPIDIOLEX		Placebo
	10 mg/kg/day	20 mg/kg/day	
	N=75 %	N=238 %	N=227 %
Hepatic Disorders			
Transaminases elevated	8	16	3
Gastrointestinal Disorders			
Decreased appetite	16	22	5
Diarrhea	9	20	9
Weight decreased	3	5	1
Gastroenteritis	0	4	1
Abdominal pain, discomfort	3	3	1
Nervous System Disorders			
Somnolence	23	25	8
Sedation	3	6	1
Lethargy	4	8	2
Fatigue, malaise, asthenia	11	12	4
Insomnia, sleep disorder, poor quality sleep	11	5	4
Irritability, agitation	9	5	2
Aggression, anger	3	5	<1
Drooling, salivary hypersecretion	1	4	<1
Gait disturbance	3	2	<1
Infections			
Infection, all	41	40	31
Infection, viral	7	11	6
Pneumonia	8	5	1
Infection, fungal	1	3	0
Infection, other	25	21	24
Other			
Rash	7	13	3
Hypoxia, respiratory failure	3	3	1

Description of other selected adverse reactions

Somnolence and sedation

39. Somnolence and sedation events have been observed in controlled trials with CBD in LGS and DS. The frequency in patients receiving 10 mg/kg/day CBD and taking clobazam was 36%. The frequency in patients receiving 20 mg/kg/day CBD and taking clobazam was 41%. Other CNS depressants, including alcohol, could potentiate the somnolence and sedation effect of CBD. The documentation states that prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on Epidiolex medicine to gauge whether it adversely affects their ability to drive or operate machinery[47].

Decreased weight

40. CBD has been shown to cause weight loss. In LGS and DS patients, the decrease in weight appeared to be dose-related, with 19% of patients taking 20 mg/kg/day CBD experiencing a decrease in weight of ≥ 5%, compared to 8% in patients taking 10 mg/kg/day CBD. In some cases, the decreased weight was reported as an adverse event. Decreased appetite and weight loss may result in

[47] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

slightly reduced height gain. Continuous weight loss/absence of weight gain should be periodically checked to evaluate if CBD treatment should be continued[48].

Haematologic abnormalities

41. CBD can cause decreases in haemoglobin and haematocrit. In LGS and DS patients, the mean decrease in haemoglobin from baseline to end of treatment was −0.37 g/dL in CBD-treated patients. A corresponding decrease in haematocrit was also observed, with a mean change of −1.4% in CBD-treated patients. Twenty-seven percent (27%) of CBD-treated patients developed a new laboratory-defined anaemia during the course of the study (defined as a normal haemoglobin concentration at baseline, with a reported value less than the lower limit of normal at a subsequent time point)[49].

Increases in creatinine

42. CBD can cause elevations in serum creatinine[50]. The mechanism has not been determined. In controlled studies in healthy adults and in patients with LGS and DS, an increase in serum creatinine of approximately 10% was observed within 2 weeks of starting CBD. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS and DS[51].

Summary of Epidiolex data

43. In the clinical pharmacological and biopharmaceutics and non-clinical reviews an overview of the data of botanical purified CBD is included. Unlike the CBD products which we know to contain a broad spectrum of other cannabinoids including THC, tetrahydrocannabivarin (THCV), cannabichromene (CBC), and their respective acids tetrahydrocannabinol acid (THCA), CBD acid (CBDA), cannabigerol acid (CBGA), tetrahydrocannabivarin acid (THCVA), delta-8 tetrahydrocannabinol (delta-8- THC), cannabidivarin (CBGV) and cannabinovarin (CBNV) (Andre *et al*., 2016) due to different extraction methods. This contains data on toxicity (hepatic), toxicokinetics, food effect, genotoxicity, drug interactions, developmental toxicity as well as reproductive toxicity. The most common side effects with Epidiolex® (which may affect more than 1 in 10 people) are somnolence (sleepiness), decreased appetite, diarrhoea, fever, tiredness and vomiting. The most common reason for stopping treatment was increased blood levels of liver enzymes (a sign of liver problems).

44. FDA's approved label for Epidiolex® recommends that physicians monitor patient liver function with blood tests[52] It is stated in that Epidiolex® must not be used in patients whose blood levels of liver enzymes are more than three times the normal limit and who also have levels of bilirubin[53] (another marker of liver problems) more than twice the normal limit[54].

[48] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[49] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[50] Creatinine is a waste product from the normal breakdown of muscle tissue. As creatinine is produced, it's filtered through the kidneys and excreted in urine. Doctors measure the blood creatinine level as a test of kidney function
[51] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[52] https://www.regulations.gov/document?D=FDA-2019-N-1482-4257
[53] Bilirubin is a yellow compound that occurs in the normal catabolic pathway that breaks down heme in vertebrates.
[54] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

Vulnerable Populations

Pregnancy

45. Studies in animals have shown reproductive toxicity (Non clinical data - Table 9). The EMA report[55] states that: As a precautionary measure, CBD should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

46. With regard to fetal harm, there is limited research on effects of CBD on embryonic development. The Epidiolex® FDA approval package contained animal data (Non clinical data - Table 9) from several species suggesting fetal toxicity was present in several animal models given CBD at clinically relevant doses. As no human data exists, FDA has advised caution and monitoring for pregnant women using Epidiolex®/CBD[56].

Breastfeeding

47. There are no clinical data on the presence of CBD or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

48. Studies in animals have shown toxicological changes in lactating animals (rabbits and rats), when the mother was treated with CBD (Non clinical data - Table 9).

49. There are no human studies on excretion of CBD in breast milk. EMA Assessment Product report[57] states that: Given that CBD is highly protein bound and will likely pass freely from plasma into milk, as a precaution, breast-feeding should be discontinued during treatment.

Fertility

50. No human data on the effect of CBD on fertility are available. No effect on reproductive ability of male or female rats was noted with an oral dose of up to 150 mg/kg/day CBD (Non clinical data - Table 8).

Older patients (65 years of age and above)

51. The safety and efficacy of CBD in patients ≥ 65 years of age have not been established.

52. In the EMA Assessment report[58] it stated: In general, dose selection for an older patient should be cautious, usually starting at the low end of the dosing range,

[55] https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf
[56] https://www.fda.gov/consumers/consumer-updates/what-you-should-know-about-using-cannabis-including-cbd-when-pregnant-or-breastfeeding
[57] https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf
[58] https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf

reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other concurrent therapy.

Renal impairment

53. CBD can be administered to patients with mild, moderate, or severe renal impairment without dose adjustment (Table 7). There is no experience in patients with end-stage renal disease. It is not known if CBD is dialyzable[59].

Hepatic impairment

54. CBD does not require dose adjustment in patients with mild hepatic impairment (Child-Pugh[60] A). Caution should be used in patients with moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C). A lower starting dose is recommended in patients with moderate or severe hepatic impairment. The dose titration should be performed as detailed in Table 7 below.

Table 7. Dose adjustments in patients with moderate or severe hepatic impairment

Hepatic Impairment	Starting Dose	Maintenance Dose	Maximum Recommended Dose
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)	2 mg/kg twice daily (4 mg/kg/day)*

*Higher doses of cannabidiol may be considered in patients with severe hepatic impairment where the potential benefits outweigh the risks.

Paediatric population

55. There is no relevant use of CBD in children aged below 6 months. The safety and efficacy of CBD in children aged 6 months to 2 years have not yet been established. No data are available.

Study participants

56. Patients had to be aged 2–55 years with a clinical diagnosis of LGS in order to be eligible for the trials.

57. Patients had to meet specific criteria including the following: patients were ineligible if they had used recreational or medicinal cannabis, or synthetic cannabinoid-based medications, within 3 months prior to screening and were to abstain from taking them during the trial. Patients were also ineligible if they had a history of alcohol or substance abuse, if they had known or suspected hypersensitivity to any ingredients of the investigational product, or if they did not meet laboratory and clinical health requirements at screening or baseline.

[59] Dialyzable: capable of diffusing through a dialyzing membrane.
[60] In medicine, specifically gastroenterology, the Child–Pugh score (or the Child–Turcotte–Pugh score or Child Criteria) is used to assess the prognosis of chronic liver disease, mainly cirrhosis.

58. The breakdown of patient characteristics is in Table 8 below.

Table 8. Characteristics of study participants

Characteristic	Total
Age (years)	
n	171
Mean (SD)	15.381
Median	13.873
Min, Max	2.72, 45.09
Age Group [n (%)]	
2-5 years	23 (13.5)
6-11 years	53 (31.0)
12-17 years	37 (21.6)
18-55 years	58 (33.9)
Sex [n (%)]	
Female	83 (48.5)
Male	88 (51.5)

59. The Secretariat is aware of some trials with human volunteers too but no statistics currently available.

Non-Clinical Data

Table 9. Animal Studies (Non-Clinical)

Study/ Species/ Test system	Dose/Effects report	Reference
Mouse study GWTX1503, 13 week oral toxicity	Mean alanine amino transaminase/alanine aminotransferase (ALT) levels were higher than controls during Week 7 and 13 in males given ≥ 150 mg/kg/day (by approximately 65% and 40%, respectively) and during Week 7 for females given 150 or 300 mg/kg/day (by 259% or 83%, respectively). Microscopic centrilobular hepatocyte hypertrophy in all animals given 300 mg/kg/day and in some animals given 100 or 150 mg/kg/day was associated with increased liver weight in all groups and macroscopic enlargement at ≥ 150 mg/kg/day. No observed adverse effect level (NOAEL) was 300 mg/kg/day CBD-OS, corresponding to the respective Week 13 maximum measured plasma concentration (C_{max}) and area under the concentration-time curve calculated to the last observable concentration at time *t* (AUC(0-t)) values of 9810 ng/mL and 44300 ng h/mL in males and 5770 ng/mL and 46400 ng h/mL in females.	EMA[61] FDA[62]
Rat GWTX1412, 26-week oral toxicity study with 4-week recovery	The centrilobular hypertrophy in the liver of animals given ≥ 50 mg/kg/day, the main finding in this study, was associated with increased liver weight, macroscopic enlargement, and, in animals given 150 mg/kg/day, increases in ALP and ALT activities. Thyroid follicular hypertrophy in both sexes, correlated with increased thyroid weights and macroscopic enlargement in males, was considered an indirect effect of treatment due to its recognized relationship with liver hypertrophy.	EMA[63]

[61] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[62] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000PharmR.pdf
[63] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf

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<tr><th colspan="8">Group Mean Plasma Toxicokinetic Parameters for CBD (GWTX1412)</th></tr>
<tr><th></th><th></th><th colspan="3">Day 1</th><th colspan="3">Week 13</th></tr>
<tr><th>Dose mg/kg/day</th><th></th><th>C_{max} ng/mL</th><th>t_{max} hour</th><th>$AUC_{(0-t)}$ ng·h/mL</th><th>C_{max} ng/mL</th><th>t_{max} hour</th><th>$AUC_{(0-t)}$ ng·h/mL</th></tr>
<tr><td>15</td><td>M</td><td>388</td><td>2.0</td><td>1140</td><td>908</td><td>4.0</td><td>5370</td></tr>
<tr><td></td><td>F</td><td>408</td><td>2.0</td><td>1380</td><td>1460</td><td>2.0</td><td>6110</td></tr>
<tr><td>50</td><td>M</td><td>2180</td><td>2.0</td><td>8750</td><td>4480</td><td>2.0</td><td>29900</td></tr>
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<tr><th></th><th></th><th colspan="3">Week 20</th><th colspan="3">Week 26</th></tr>
<tr><td>15</td><td>M</td><td>1160</td><td>2.0</td><td>4510</td><td>1400</td><td>4.0</td><td>8700</td></tr>
<tr><td></td><td>F</td><td>2230</td><td>2.0</td><td>5460</td><td>2070</td><td>2.0</td><td>10800</td></tr>
<tr><td>50</td><td>M</td><td>5580</td><td>4.0</td><td>26200</td><td>5240</td><td>2.0</td><td>36700</td></tr>
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<tr><td></td><td>F</td><td>10400</td><td>2.0</td><td>36200</td><td>7530</td><td>4.0</td><td>67500</td></tr>
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Some further effects of hormonal dysregulation were observed across the studies with CBD or impurities (structurally very similar to CBD) such as small testes with unsuccessful impregnation of the dam (Peri-Postnatal developmental (PPND) study in rats at the high dose), interstitial cell hyperplasia of ovary in rats (26-week study in rats with CBD-OS), or an increased incidence of the dioestrus/metoestrus phases of cycle.

In addition, triiodothyronine (T3), T4 and thyroid-stimulating hormone (TSH) endpoints in this repeat dose study, was provided as draft results to address the underlying effects causing discrepancies in hormonal pathways. Dose-dependent decrease in T4 and increase in TSH has been noted mostly in male rats and in individual female rats. In general, rodents are more sensitive than humans to thyroid perturbation effects. It is however agreed with the applicant that monitoring for potential hormonal disturbance via clinical and pharmacovigilance activities should be initiated, if the final non-clinical and/or available clinical data demonstrates a cause for concern regarding endocrine parameters.

Final study report (GWTX18002) with characterization of potential risk due to hormonal disturbances is awaited via post-authorization measure commitment.

Toxicity effects were observed in lungs with dose-related increase in incidence and severity of pulmonary foamy macrophages observed across studies in rat with CBD. These of findings are deemed toxicologically insignificant and not relevant to humans. No associations to other pulmonary adverse effects in non-clinical or clinical studies have been detected.
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<td>39-Week Oral (Gavage) Toxicity with 4-Week Recovery in Dogs (GWTX1413)</td>
<td>Beagle dogs (4/sex/main groups) received CBD-OS at 0 (vehicle), 10, 50, or 100 mg/kg/day once daily for 39 weeks. Reversibility of changes was evaluated following a 4-week recovery phase (2/sex/control and high dose groups).

In dogs, the target organ for toxicity was liver with hepatocyte hypertrophy, macroscopic enlargement and increased liver weight. No increase in bilirubin, necrosis or significant inflammation and/or proliferation suggests that effects observed in rats and dogs might be reflections of adaptive changes due to microsomal hepatic induction. However, due to absence of hormonal examinations and some other effects of hormonal misbalance observed in the studies these effects need to be further substantiated via post-authorisation measure.</td>
<td>EMA[64]</td>
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<tr>
<td>GWTX1503</td>
<td>100, 150, 300 mg/kg CBD-OS 13 weeks</td>
<td>EMA[65]</td>
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[64] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[65] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf

BioA not GLP CD-1 mice/12	NOAEL (mg/kg/ day): 300 mg/kg Liver centrilobular hypertrophy in some animals given 100 or 150 mg/kg/day and all animals given 300 mg/kg/day Liver centrilobular hyper-trophy at ≥ 50 mg/kg/day Doses ≥ 50 mg/kg/day	
GWTX1412 BioA not GLP Wistar/10 or 15	15, 50, 150 mg/kg CBD-OS 26 weeks + 4 weeks recover NOAEL (mg/kg/ day): 150 mg/kg Thyroid hypertrophy in both sexes and increased adrenocortical vacuolation in males. Pale foci in lungs, increase in pulmonary foamy macrophages	EMA[66]
GWTX1413 BioA not GLP Beagle dog/4-6	10, 50, 100 mg/kg CBD-OS 39 weeks + 4 weeks recovery NOAEL (mg/kg/ day): 100 mg/kg/day Hepatocyte hypertrophy at ≥ 10 mg/kg/day associated with increased liver weight.	EMA[67]
GWTX1578 BioA not GLP Wistar/10	30, 35, 50 mg/kg purified CBD i.v. 10 min infusion 14 days NOAEL (mg/kg/ day): 50 mg/kg/day Post-dose observations were low gait, staggering, and underactivity in animals given ≥ 35 mg/kg/day; and tremors, slow deliberate movements, subdued/sluggish at 50 mg/kg/day	EMA[68]
GWTX1579 BioA not GLP Beagle dog/3	3, 6, 9, 15 mg/kg purified CBD by intravenous bolus 14 days NOAEL (mg/kg/ day): 15 mg/kg Post-dose observations at all dose levels were associated with an "anaphylactoid-type" response to the vehicle. Diffuse hepatocellular vacuolation at ≥ 6 mg/kg/day	EMA[69]
	Genotoxicity	
Gene mutations in bacteria (GWOR0910/GLP) Salmonella strains TA98, TA100, TA1535, TA1537, and TA102	1.6 – 320 µg purified CBD/plate +/- S9 Negative	EMA[70]
Chromosomal aberrations *in vivo* (GWOR0903/GLP) Rat, micronuclei in bone marrow	125, 250, 500 mg/kg CBD-OS Negative	EMA[71]
DNA damage *in vivo* (GWTX1510/GLP) Rat Alkaline COMET Assay	125, 250, 500 mg/kg CBD -OS Negative	EMA[72]
	Reproductive Toxicity	
Male fertility GWTX1456/GLP	75, 150, 250 mg/kg/day (2 weeks prior to pairing up to review of female pregnancy data)	EMA[73]

[66] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[67] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[68] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[69] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[70] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[71] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[72] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[73] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf

Wistar rat/20	No effects on male reproductive organ weights NOAEL (mg/kg): 250 mg/kg/day	
Female fertility GWTX1456/GLP Wistar rat/20	75, 150, 250 mg/kg/day 2 weeks prior to pairing up to gestation day 6 No effect on female reproductive indices, female oestrus cycling or pregnancy parameters NOAEL (mg/kg): 250 mg/kg/day	EMA[74]
Embryo-fœtal development GWTX1455/ nonGLP Wistar/6 DRF study	150, 250, 300 mg/kg/day gestation day 6 to 17 No adverse effects at lower doses Increased preimplantation loss at 300 mg/kg/day 300 mg/kg/day: One dead rat, weight loss of 32% of controls Increased preimplantation loss at 300 mg/kg/day No adverse effects at lower doses NOAEL F0: 250 mg/kg/day F1: 250 mg/kg/day (mg/kg)	EMA[75]
Embryo-fœtal development GWTX1454/GLP Wistar/20	75, 150, 250 mg/kg/day gestation day 6 to 17 Complete litter loss of 2/20 dams at 250 mg/kg/day NOAEL (mg/kg): F0: 150 mg/kg/day F1: 150 mg/kg/day	EMA[76]
Embryo-fœtal development DRF GWTX1453/ Non-GLP Rabbit/6	50, 80, 125 mg/kg/day gestation day 7 to 19 Body weight loss compared to controls in dams Dose Range Finding (DRF) study	EMA[77]
Embryo-fœtal development DRF GWTX1452/ GLP Rabbit/22	50, 80, 125 mg/kg/day gestation day 7 to 19 Unossified metacarpal, bulging eyes, and nonerupted incisors) were considered to be secondary to the reduced fetal weights at 125 mg/kg/day NOAEL (mg/kg): F0: 80 mg/kg/day F1: 80 mg/kg/day	EMA[78]
Pre & postnatal development GWTX1532/GLP Rat/22	75, 150, 250 mg/kg/day Gestation day 6 to lactation day 21 F1 males: Small testes F1 female: Reduced fertility indices NOAEL (mg/kg): F0: 250 mg/kg/day F1: 75 mg/kg/day	EMA[79]
	Fertility and early embryonic development	
Fertility and early embryonic development toxicity study (GWTX1456)Han Wistar rats (20/sex/group)	0, 75, 150, or 250 mg/kg/day for 2 weeks prior to pairing until the day prior to necropsy for males and up to gestation day 6 for females There were no treatment-related deaths and no adverse clinical or post-dosing observations. During the post-pairing phase, there was a treatment-related reduction in the overall body weight gain of males given ≥ 150 mg/kg/day. There were no treatment-related necropsy observations in either sex and no test article-related effects on male or female reproductive indices, male reproductive organ weights, female oestrus cycling, or any caesarean-section parameters at doses up to 250 mg/kg/day Purified CBD, which was	EMA[80]

[74] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[75] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[76] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[77] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[78] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[79] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[80] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf

	determined to be the NOAEL. Evaluation of CBD effects on male and female reproductive performance is considered adequate and it is agreed that no significant negative effects were observed in rat. A safety margin of 60 fold were calculated for inclusion in the Summary of Product Characteristics (SmPC) based on exposure measurements from the rat embryofetal study (GWTX1454) at 250 mg/kg/day dose level on gestation day 17. Adjusted human AUC(0-24h) 2790 ng h/ml was used for calculation.	
	Embryo-foetal development	
	Embryo-foetal development was evaluated in rat and rabbit. Rabbit seemed to be more sensitive to effects of CBD compared to rat. This was evident by the observed dose-dependent body weight loss compared to controls in rabbit. Embryo-foetal development in rat was insensitive to high CBD exposure (C_{max} up to 12800 ng/ml). The NOAEL for maternal toxicity was amended to 150mg/kg/day due to 100% loss of pregnancy in 2 dams at the high dose of 250 mg/kg/day. NOAEL for effects on embryofoetal development in rabbit was 80 mg/kg/day. Foetal variations observed at 125 mg/kg/day CBD (*e.g.*, unossified metacarpal, bulging eyes, and nonerupted incisors) were considered to be secondary to the reduced foetal weights. Maternal exposure at 80 mg/kg/day Purified CBD corresponded to gestation day 19. C_{max} and AUC(0-t) values of 220 ng/mL and 2030 ng h/ml, respectively. C_{max} of this dose was lower than pharmacological relevant exposure in children and adults (approximately 290 ng/ml and 320 ng/ml, respectively). However, protein binding is lower in rabbit compared to rats and humans with 65% bound in rabbit and 95% and 94% in rat and humans, respectively. The non-existing safety margins for the rabbit study are reflected in SmPC section 5.3. and the rat NOAEL of 150 mg/kg/day is reflected to result in a safety margin of 50 fold.	EMA[81]
	Prenatal and postnatal development, including maternal function	
GWTX1532 Female Wistar Rats	The effects of CBD on pre- and postnatal development including maternal function were evaluated in rat. Female Wistar (Han) rats (22/grp) were given oral (gavage) doses of Purified CBD (0 (sesame oil vehicle), 75, 150, or 250 mg/kg/day; 5 mL/kg) from gestation day 6 to PND 2. There were no Purified CBD- related clinical or post dosing observations for the maternal animals (F0). Endpoints in F1 generation included body weight, developmental landmarks including sexual development, learning and memory, fertility and macroscopic examination at necropsy. NOAEL was lower for F1 generation (75 mg/kg/day) than for the parental generation (250 mg/kg/day) due to small testes in males and reduced fertility index in females of F1 generation. Dosing of the maternal animals at mid dose and high dose in PPND study in rats (GWTX1532) had a direct effect on progeny exposed to the drug via placenta prenatally or postnatally via milk. In F1 generation physical, sexual and developmental delay with effects on neurobehavioral functions (pupillary response) were observed. CBD is a lipophilic compound with long elimination half-life and thus is expected to be excreted significantly to milk. No data on CBD analysis in milk was provided. However, published data on CBD and Sativex indicate very high milk to plasma ratio. Breast-feeding is not recommended during treatment and due to severity of the proposed indications discontinuation of the therapy during lactation is out of question. Thus, breast-feeding should be discontinued during treatment. A Safety margin of 9 was calculated for this study, based on exposure data from Study GWTX1454, at 75 mg/kg/day, on GD6. Adjusted human AUC(0-24h) 2790 ng h/ml was used for calculation of the safety margin.	EMA[82]
	Carcinogenicity	

[81] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[82] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf

A 104 weeks carcinogenicity study / Rats	CBD by the oral dietary route of administration at doses 5, 15, or 50 mg/kg/day. No concerns of tumour findings were found. Interestingly, at 50 mg/kg/day CBD there was a reduced incidence of tumours generally associated with hormonally-mediated neoplasia in aging animals. The clinical relevance of this finding is uncertain. It was noted that what was remarkable for this study is the increase in exposure of CBD over time. This trend was also observed in the 26 weeks repeat dose toxicity study in rat, especially from week 20 to 26. The carcinogenic potential of CBD has been adequately evaluated to be negative and the liver findings of the repeat dose toxicity studies was confirmed at lower doses in rat at life-time exposure.	EMA[83]

Other relevant information

FDA November 2019 statement

60. A statement was recently published by the FDA: *What You Need to Know (And What We're Working to Find Out) About Products Containing Cannabis or Cannabis-derived Compounds, Including CBD*[84] that highlighted some of the potential adverse effects of CBD.

Risk Assessment

Approach to risk assessment

61. As noted previously, assessment of a medicine will balance the benefits against the risk of side effects in a way which would not be done for food ingredients. In the GW Pharmaceutical statement on the submission of scientific data it states the following[85]: "In the case of CBD, 5 mg/kg/day is not a safe dosage and causes an unacceptable safety signal outside of a clinical setting where there is a benefit risk consideration. This clear safety signal cannot be offset by historical use patterns in the general population because there is no historical use of CBD or hemp extract as a food. Therefore, substantial safety factors need to be applied to this LOAEL and may include: a chronicity factor of 10-fold, inter-subject variability of 10-fold, and a LOAEL to NOAEL factor of three- to 10-fold". In addition, medicines are prescribed under medical supervision and may recommend, for example, monitoring of patients' liver function enzymes.

62. Using conventional methods that would be applied to food ingredients or contaminats, a risk assessment could be done for CBD using a LOAEL from the available data in human volunteers or a NOAEL from the available animal data as a point of departure, as follows.

[83] https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[84] https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis
[85] https://www.regulations.gov/document?D=FDA-2019-N-1482-4257

Human data

63. Liver effects have been reported in some human volunteers at doses of 5 mg/kg bw/day- (equivalent to 350 mg/day for a 70 kg adult). This would be considered to be a LOAEL.

Applying the conventional uncertainty factor (UF) for inter-subject variability (10 factor):
5 mg/kg/ 10 = 0.5 mg/kg

Then extrapolating a LOAEL to NOAEL (generally a factor of 3):

0.5 mg/kg / 3= 0.17 mg/kg- equivalent to 11.7 mg/day for a 70 kg adult.

Since the substance accumulates and there are no chronic data in humans, an extra uncertainty factor for lack of chronic data *i.e.* chronicity factor could be appropriate:

0.17 mg/kg / 3 =0.06 mg/day - equivalent to 4 mg/day for a 70 kg adult.

Animal Data

64. Several risk assessment approaches could be taken using the available animal data.

Liver toxicity

65. Health Based Guidance Values (HBGV) could be based on animal data but in this case, the No Observed Adverse Effect Level for liver effects in rats is 150 mg/kg body weight, applying the usual uncertainty factors of 10 x10 would give 1.5 mg/kg bw equivalent to 105 mg/day in a 70 kg adult. This suggests that humans may be more sensitive than animals since we know that this dose would result in effects in some sensitive human volunteers.

66. From the 26 week oral rat study whereby the NOAEL is 150 mg/kg bw/day

Then applying the inter-subject and inter individual uncertainty factors (10 x 10) = 150/100= 1.5 mg/kg/bw day, equivalent to 105 mg/day for a 70 kg adult.

Reproductive toxicity

150 A package of reproductive toxicity studies has been submitted. These indicated no adverse effects on male and female fertility indices at doses up to 250 mg/kg CBD. However, adverse effects were reported in embryo-fetal developmental studies including pre-implantation loss, litter loss, reduced fetal weight and reduced testes size and fertility indices in females in the F1 generation. The NOAELs for these latter studies were 80 and 75 mg/kg bw, respectively.

151 From the study whereby the NOAEL is 75 mg/kg bw/day:

Applying the inter-subject and inter individual uncertainty factors (10 x 10) =

75/100= 0.75 mg/kg/bw day equivalent to 52.5 mg/day for a 70 kg adult.

Chronic toxicity

152 No adverse effects were apparent in rats treated with 50 mg/kg bw/day CBD. This would result in a potential HGBV of 50/10x10 = 0.5 mg/kg/bw per day which is equivalent to 35 mg/day in a 70 kg adult.

153 Very little data from this study is publicly available and it is was not conducted to Good Laboratory Practice (GLP) and so it is unclear what conclusions can be drawn. The FDA[86] considered the study to be inadequate, stating that "...only the CBD Botanical Drug Substance (BDS) was administered in the diet, resulting in uncertain exposures, potential interactions with impurities, and excessive BW effects in the single species tested is also an important deficiency. This may at least partially be addressed by the mouse study that is currently underway. The toxicity evaluation of the parent compound can otherwise be considered adequate". No Special Protocol Assessment[87] (SPA) was submitted for this study.

154 These risk assessments would apply to the CBD component only and not to the related cannabinoids that may be present. These may be more or less harmful than CBD, but this is presently unknown.

Further considerations

CBD Nanoemulsions/ CBD NanoDelivery Technology

155 As stated in the scoping paper presented to the COT in July 2019[88], some new CBD oils are now nano encapsulated for maximum uptake efficacy. CBD is highly lipophilic, hydrophobic and its oral bioavailability[89] is known to be very low in humans. As a result, companies are starting to use CBD Nanoemulsions/ CBD NanoDelivery Technology to enhance uptake/bioavailability as well as to be easily mixed into beverages. This nano encapsulated CBD oil uses liposomes at the nano scale (<100nm) which are artificially constructed vesicles consisting of a phospholipid bilayer (Nakano *et al*., 2019). These "nano-cannabinoids" are now marketed as "water-soluble CBD" for maximum absorption.

156 The proposed risk assessment applies to CBD in a form consistent with Epidiolex so changes to increase bioavailability will add to the uncertainties.

Summary and discussion

157 This paper provides an update on the medicinal data for purified botanical CBD which is publicly available.

[86] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000PharmR.pdf
[87] Special Protocol Assessment Guidance for Industry | FDA
[88] https://cot.food.gov.uk/sites/default/files/tox2019-32.pdf
[89] Bioavailability: the proportion of a drug or other substance which enters the circulation when introduced into the body and so is able to have an active effect.

158 In humans, the most common adverse reactions in humans are somnolence, decreased appetite, diarrhoea, pyrexia, fatigue, and vomiting. The most frequent cause of discontinuations was transaminase elevation. Studies in animals have also shown transaminase elevation, liver injury as well as reproductive toxicity.

159 It is hoped that the data on Epidiolex may be enough to undertake a provisional risk assessment based on the CBD (>98% purity) component only. This would assist the FSA in decision making in relation to CBD products. The risk assessment is described as provisional since only limited data are in the public domain and it would only apply to CBD, and not the other cannabinoids or other components that might be present in CBD products due to different manufacturing methodologies. The provisional assessment could be revised when new data become available.

160 It is important to note that the safety profile of food grade CBD might be different to medical grade products due to differences in composition and production. Products may also be formulated in such a way to enhance uptake.

161 In humans, adverse liver effects were observed at 5 mg/kg/day and there may be possible effects at 1 mg/kg/day. As stated on the GW Pharmaceutical statement:

“5 mg/kg/day of CBD is not a safe dosage and causes an unacceptable safety signal outside of a clinical setting where there is a benefit risk consideration.”

162 In animals, adverse liver and reproductive effects have been reported, the NOAELs being 150 and 75 mg/kg bw, respectively. A chronic study is available but only limited details are publicly available and it was considered inadequate by the US FDA.

163 The data suggest that humans might be more sensitive to the adverse effects of CBD than laboratory animals.

164 Other uncertainties might be the lack of chronic data *i.e*. long term effects of CBD in humans, the lack of data on lactation, the interaction with other cannabinoids/botanicals as well as other medicines or compounds such as alcohol and the lack of data in some vulnerable groups such as older people.

165 CBD has the potential to accumulate due to its lipophilic properties.

Conclusions

166 A possible provisional risk assessment has demonstrated that a HBGV of 0.06 mg/kg bw/day (4 mg/day in a 70 kg adult) would be the maximum acceptable daily dose derived from a LOAEL in humans.

167 This would apply to CBD only and not the related cannabinoids that may be present and these may be more or less active than CBD itself.

168 It is uncertain whether such a level would be applicable to vulnerable groups such as pregnant women.

Questions for the Committee

i) Do the Committee have any comments on the safety of CBD in humans based on the data presented? In particular, do they have any comments on the potential for transaminase elevations, drug interactions and somnolence.
ii) Do the Committee have any comments on the safety of CBD in laboratory animal studies based on the data presented? In particular, do they have comments on the adverse effects on the liver and the reproductive system?
iii) Can any conclusions be drawn on long term intake of CBD in humans or animals?
iv) Do the Committee have any comments on the potential for reproductive effects in humans?
v) Do these new data on medicinal CBD provide enough information for a provisional risk assessment to be conducted that could apply to the CBD in other products?
vi) If so, should the human or animal data be used and what would the appropriate UFs be?
vii) If it is not possible to do a provisional risk assessment, is it possible to identify an intake of CBD that would not result in adverse effects? Is it possible to identify an intake of CBD where adverse effects would be expected?
viii) Do Members have any other comments?

Secretariat
January 2020

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Abbreviations

AEs	adverse events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BDS	Botanical Drug Substance
bw	bodyweight
CBD	cannabidiol
CBD-OS	CBD Oral Solution
CBC	cannabichromene
CBDA	cannabidiol acid
CBGV	cannabidivarin
CBNV	cannabinovarin
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and The Environment
COM	Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment
Cmax	Maximum Concentration observed
CNS	central nervous system
delta-8- THC	delta-8 tetrahydrocannabinol
DILI	drug induced liver injury
DRF	Dose Range Finding
DS	Dravet Syndrome
EMA	European Medical Agency
FDA	Food and Drug Administration
FSA	Food Standards Agency
GI	gastrointestinal
GGT	gamma glutamyltransferase
GLP	good laboratory practice
HBGV	Health Based Guidance Values
LGS	Lennox-Gastaut syndrome
LOAEL	Lowest Observed Adverse Effect Level
NOAEL	No observed adverse effect level
PK	pharmacokinetic
PPND	Peri-Postnatal developmental
RCTs	randomized controlled trials
TEAS	treatment emergent adverse events
TE	treatment emergent
TSH	thyroid-stimulating hormone
Tmax	Time of Maximum concentration observed
t½	half-life
THCVA	tetrahydrocannabivarin acid
THCA	tetrahydrocannabinol acid
THC	tetrahydrocannabinol
THCV	tetrahydrocannabivarin

UF	uncertainty factor
ULN	upper limit of normal
U.S.	United States
VPA	valproate

ANNEX A

Center for Drug Evaluation and Research

On the Epidiolex approval package online page[90] there are the following reviews by the Center for Drug Evaluation and Research (CDER):

- summary review[91]
- product quality review[92]
- statistical review[93]
- non clinical review[94]
- clinical pharmacological and biopharmaceutics[95]
- risk assessment and risk mitigation review[96]
- other reviews[97]

European Medicine Agency

In September 2019, the European Medical Agency (EMA) approved CBD oral solution *i.e.* first plant-derived cannabis-based medicine and published a full public assessment report[98].

GW Pharma Scientific Submission

GW Pharmaceuticals' Submission on Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds was published in July 2019[99].

Additional PK information

Table 1. Summary of Mean C_{max} for CBD and the Metabolites for Different Dosing Scenarios (taken from the Other Reviews FDA report[100])

[90] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm
[91] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000SumR.pdf
[92] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000ChemR.pdf
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[99] https://www.regulations.gov/document?D=FDA-2019-N-1482-4257
[100] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000OtherR.pdf

			Mean Cmax (ng/mL)			
Dosing in HV	Food status for dos	Timing	CBD	6-OH-CBD	7-OH-CBD	7-COOH-CBD
750 mg SD (TQT)	Fasted	Day 1	387	5	94	1872
4500 mg SD (TQT)	Fasted	Day 1	629	12	234	4621
1500 mg SD (FE)	Fasted	Day 1	335	10	135	2426
	Fed (High fat-high calorie meal)	Day 1	1628	27	393	5044
750 mg BID MD (10 mg/kg BID dosing for a 75 kg subject)	Fasted*	Day 1 AM	291	8	123	2785
		Day 1 PM	732	15	197	5307
		Day 7 AM (~Steady State AM sampling)	330	13	153	9824
	Fed (High fat-high calorie meal)**	Day 1 AM	1410	23	358	5793
		Day 1 PM	3552	43	574	11039
		Day 7 AM (~Steady State AM sampling)	1602	36	444	20434

HV= Healthy adult volunteers; SD= Single dose; MD= Multiple dosing; FE= Food effect Study GWEP1544; TQT= TQT Study GWEP1541

*Data from Study GWEP1544 (MD)

**Data estimated by the sponsor using fasting data from GWEP1544 and applying an analyte specific 'food effect factor' determined in GWEP1544 [CBD 4.85, 6-OH 2.80, 7-OH 2.91, 7-COOH 2.08]

Table 2. CBD Pharmacokinetic Parameters (PK Set) (taken from the EMA report)

Parameter	Geometric mean (Geometric CV%)[a]			
	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)	Normal Hepatic Function (n=8)
C_{max} (ng/mL)	233.08 (70.51)	354.15 (42.33)	380.94 (52.22)	148.00 (64.97)
$AUC_{(0-\infty)}$ (h*ng/mL)[c]	699.48 (44.18)	1162.70 (39.88)	2438.53 (29.54)[b]	473.68 (73.83)
$AUC_{(0-t)}$ (h*ng/mL)	648.09 (44.24)	1054.15 (38.90)	1855.10 (51.99)	449.08 (73.50)
CL/F (L/h)	285.93 (44.18)	172.01 (39.88)	82.02 (29.54)[b]	422.23 (73.83)
V_z/F (L)	5302.44 (60.06)	4668.44 (40.13)	2437.09 (70.52)[b]	4105.49 (37.50)
t_{max} (h)	2.8 (1.5-5.0)	2.0 (1.5-3.0)	2.5 (2.0-5.0)	2.3 (1.5-5.0)
$t_{½}$ (h)[d]	15.68 (58.31)	20.47 (39.19)	22.05 (44.94)[b]	8.58 (68.38)
$C_{max(u)}$ (ng/mL)	10.42 (83.24)	27.51 (119.04)	36.96 (120.60)	9.99 (63.41)
$AUC_{(0-\infty)(u)}$ (h*ng/mL)[c]	31.27 (58.48)	90.32 (118.21)	269.56 (89.72)	31.98 (76.73)
$AUC_{(0-t)(u)}$ (h*ng/mL)	28.98 (58.34)	81.89 (119.29)	180.01 (126.70)	30.32 (76.71)
$CL_{(u)}$/F (L/h)	12.78 (79.62)	13.36 (64.47)	9.07 (71.55)[b]	28.51 (87.94)
$V_{z(u)}$/F (L)	237.08 (85.25)	362.65 (58.71)	269.40 (128.11)[b]	277.18 (42.83)

[a]Except for tmax where median and range are shown and t½ where arithmetic mean and %CV are shown.
[b]n=5.
[c]Percent extrapolation ≤ 30% was required to retain AUC(0-∞) for unbound and total fractions; ***subjects that did not satisfy this criterion were excluded from the analysis.***
[d]Percent extrapolation ≤ 30% and r2> 0.80 was required to retain t½; subjects that did not satisfy ***these criteria were excluded from the analysis.***

Table 3. Pharmacokinetic Parameters of CBD, 6-OH-CBD, 7-OH-CBD and 7-COOH-CBD (Taken from Clinical Pharmacology and Biopharmaceutics Review FDA[101]).

[101] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000ClinPharmR.pdf

GWP42003-P Dose (n)	C_{max} (ng/mL)[a]	t_{max} (h)[b]	$AUC_{(0-t)}$ (ng.h/mL)[a]	$AUC_{(0-\infty)}$ (ng.h/mL)[a]	$\%AUC_{extra}$[c]	CL/F (L/h)[c]	V_z/F (L)[c]	$t_{½}$ (h)[c]
CBD								
750 mg (n=49)	387 (52.4)	5.00 (3.00–8.00)	1960 (43.4)	2150 (38.2)[d]	4.87 (49.0)[d]	375 (42.1)[d]	2820 (46.9)[d]	5.94 (53.2)[d]
4500 mg (n=48)	629 (74.5)	4.01 (2.00–12.00)	3143 (77.1)	3365 (75.6)[d]	7.21 (53.6)[d]	1729 (96.0)[d]	19261 (75.8)[d]	8.55 (38.0)[d]
6-OH-CBD								
750 mg (n=49)	5.34 (54.8)	4.00 (1.00–6.03)	38.7 (113.1)	55.5 (68.1)[j]	21.53 (27.7)[j]	NC	NC	13.9 (92.6)[e]
4500 mg (n=48)	11.9 (69.2)	4.02 (1.00–12.00)	74.9 (100.9)	97.6 (80.5)[k]	15.17 (38.1)[k]	NC	NC	9.30 (82.8)[f]
7-OH-CBD								
750 mg (n=49)	93.9 (57.2)	4.02 (2.00–6.03)	719 (47.3)	913 (43.9)[l]	18.16 (37.9)[l]	NC	NC	12.2 (49.9)
4500 mg (n=48)	234 (61.9)	4.52 (2.00–12.00)	1536 (63.7)	1872 (56.3)[m]	13.51 (45.9)[m]	NC	NC	11.3 (46.9)[g]
7-COOH-CBD								
750 mg (n=49)	1872 (49.1)	6.00 (4.00–23.02)	28109 (49.4)	NC	NC	NC	NC	33.3 (37.4)[h]
4500 mg (n=48)	4621 (63.5)	5.02 (4.00–18.03)	63603 (70.1)	NC	NC	NC	NC	25.1 (32.1)[i]

Source: Clinical Study Report GWEP1541, Table 8.4.3.1.3-1.

Table 3. Overview of statistically significant correlations in exploratory logistic regression of adverse events and the exposure (AUC) of the 3 analytes (taken from EMA public assessment report)

AE	AUC CBD	AUC 7-OH-CBD	AUC 7-COOH-CBD	Yes	No
ALP > 2 × ULN				11	349
ALT > 2 × ULN	++	++	+	44	316
AST > 2 × ULN	++	++		23	337
Bilirubin > 2 × ULN				0	360
Diarrhoea	+			43	317
Fatigue	+	+	+	20	340
GGT > 2 × ULN	+			107	253
Loss of appetite	++	++	++	44	316
Maculopapular rash				5	355
Nausea				9	351
Rash	+	+	+	19	341
Somnolence	++	++	++	56	304

Note: ++, $p<0.01$ and positive correlation; +, $p<0.05$ and positive correlation. Yes and No columns indicate the numbers of subjects with at least 1 of the given AE (Yes) or not (No).