19 September 2019
EMA/428872/2019
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Epidyolex (cannabidiol)
Sponsor: GW Pharma (International) B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

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1. Introductory comment

The approved therapeutic indication “Epidyolex is indicated for 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” falls within the scope of the two designated orphan conditions Lennox Gastaut syndrome and Dravet syndrome. The maintenance of the two respective orphan designations is covered in this one document.

2. Epidyolex (cannabidiol) for treatment of Lennox-Gastaut syndrome EU/3/17/1855 (EMA/OD/275/16)

2.1. Product and administrative information

Product	
Active substance	Cannabidiol
International Non-Proprietary Name	Cannabidiol
Orphan condition	Treatment of Lennox-Gastaut syndrome
Pharmaceutical form	Oral solution
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	Antiepileptics, other antiepileptics (N03AX)
Sponsor's details:	GW Pharma (International) B.V. Databankweg 26 Amersfoort 3821 AL Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	GW Research Ltd
COMP opinion date	16 February 2017
EC decision date	20 March 2017
EC registration number	EU/3/17/1855
Post-designation procedural history	
Transfer of sponsorship	Transfer from GW Research Ltd to GW Pharma (International) B.V – EC decision of 10 April 2019
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	M. Ainsworth, O. Slanař
Applicant	GW Pharma (International) B.V.
Application submission date	21 December 2017
Procedure start date	1 February 2018
Procedure number	EMEA/H/C/004675
Invented name	Epidyolex
Therapeutic indication	Epidyolex is indicated for 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. Further information on Epidyolex can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex
CHMP opinion date	25 July 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	D. Duarte, G. Capovilla
Sponsor's report submission date	18 September 2018

COMP opinion date (adoption via written procedure)	26 July 2019

2.2. Grounds for the COMP opinion at the designation stage

The sponsor GW Research Ltd submitted on 27 October 2016 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing cannabidiol for treatment of Lennox-Gastaut syndrome (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing cannabidiol was considered justified based on clinical data demonstrating reduced seizure frequency in patients who received the product on top of standard of care;
- the condition is chronically debilitating due to the high frequency of multiple types of seizures, cognitive deterioration, behavioural disturbances, and poor long termlong-term prognosis despite existing treatments;
- the condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cannabidiol will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who failed to respond to authorised products achieved a reduction of seizure frequency. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing cannabidiol as an orphan medicinal product for the orphan indication: treatment of Lennox-Gastaut syndrome.

2.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Lennox-Gastaut syndrome (LGS) is a rare epilepsy disorder characterised by the presence of multiple seizure types, slow (≤2.5 Hz) spike-waves EEG abnormalities with frequent abnormal background activity when awake and a particular EEG pattern of fast rhythms (10–20 Hz) during sleep. The seizure types vary among patients: the most invalidating are sudden drop attacks (myoclonic, atonic or myoclono-atonic) but can also include focal, tonic, tonic-clonic, atonic, atypical absence, and myoclonic seizures.

In the past, LGS was subdivided into cryptogenic and symptomatic types by the presence or absence of an underlying cause. The new classification (Scheffer et al, 2017) has introduced many other aetiological categories and this distinction is no more valid. The etiology of LGS is extensive and diverse, varying from congenital to acquired causes. Among these, frequent causes include malformations of cortical development, tuberous sclerosis, hereditary metabolic diseases, sequelae of hypoxic–ischemic encephalopathy and of other perinatal injuries, lesions secondary to inflammatory brain diseases such as encephalitis, meningitis and congenital infections as toxoplasmosis and cytomegalovirus. About one-third of LGS cases occur without antecedent history or evidence of brain pathology and these patients tend to have a better prognosis than those with brain lesions.

The sponsor acknowledged the release of a revised classification of seizure and epilepsy types in March 2017, which did not alter the classification of epilepsy syndromes (Scheffer et al, 2017). Therefore, Lennox-Gastaut Syndrome (LGS) remains a recognised electroclinical epilepsy syndrome in accordance with the 2010 ILAE classification system (Berg et al, 2010).

The approved therapeutic indication "Epidyolex is indicated for 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." falls within the scope of the designated orphan indication "Treatment of Lennox-Gastaut syndrome" in combination with the second orphan drug designation held by the sponsor for "Treatment of Dravet syndrome".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified (please also see Epidyolex EPAR).

The clinical development program supporting the efficacy of CBD-OS comprises 2 randomised, placebo-controlled trials in LGS; 1 investigating 10 and 20 mg/kg/day CBD-OS (GWEP1414) and 1 investigating 20 mg/kg/day CBD-OS (GWEP1423).

The pivotal trials consisted of a 4-week baseline period, followed by a 14-week treatment period comprising a 2-week titration (dose escalation) period and a 12-week maintenance (stable dosing) period. Patients who discontinued the investigational medicinal product (IMP) were to taper the dose over a 10-day period, with a safety follow-up 4 weeks after final dose.

The primary endpoint was met in both studies with an approximately 40-50% median drop seizures frequency in the active groups as compared to approximately 15-25% in the placebo groups:

Study GWEP1414: A greater median reduction in drop seizure frequency during the treatment period was seen in the both the 20 mg/kg/day CBD-OS (-41.86) and the 10 mg/kg/day CBD-OS (-37.16) groups, compared with the placebo group (-17.17). The estimated median difference was in favour of CBD-OS treatment over placebo for both 20 mg/kg/day CBD-OS (-21.57; 95% CI: -34.79, -6.67) and 10 mg/kg/day CBD-OS (-19.19; 95% CI: -31.24, -7.69); the difference between each CBD-OS group and placebo was statistically significant (p=0.0047 and p=0.0016, respectively).

Study GWEP1423: A greater median reduction in drop seizure frequency during the treatment period was seen in the CBD-OS group (-43.90), compared with the placebo group (-21.80). The estimated median difference was in favour of CBD-OS treatment over placebo (-17.21; 95% CI: -30.32, -4.09), and the difference between treatment groups was statistically significant (p=0.0135).

CBD-OS can cause hepatocellular injury. Across the LGS and DS pivotal trials, two patients concomitantly treated with valproate experienced toxic hepatocellular injury in combination with metabolic acidosis and encephalopathy, respectively. The incidence of TEAEs meeting the search criteria for AESI abnormal liver TEAEs was 14.9% in the All CBD-OS group (N=456) compared with 3.1% in the placebo group (N=292). However, the number of liver-related adverse events was strongly dose-dependent.

Currently available antiepileptic treatment rarely succeeds in keeping the children free of seizures and the risk of sudden unexpected death in epilepsy (SUDEP) remains high. In that respect, the statistically significant reduction in seizure frequency offered by CBD-OS constitutes a favourable effect in this difficult to treat population. A reduction of 50% in the frequency of seizures is considered a clinically relevant effect. However, some notable uncertainties about the favourable effect of CBD-OS remain. In particular, results of the subgroup analysis of patients treated with clobazam compared to patients treated without clobazam, indicated that there is residual statistical uncertainty regarding the treatment effect of cannabidiol in patients not taking clobazam. In this population, efficacy has not been established. Therefore, the indication proposed by the CHMP was narrower than originally proposed by the sponsor.

Chronically debilitating and/or life-threatening nature

Since the orphan designation application (ODA) was submitted on 27 October 2016 and the COMP recommended granting orphan designation on 16 February 2017, no significant changes in the chronically debilitating and/or life-threatening nature of the condition have been described since no new treatment guidelines or major reviews on LGS have been identified in the literature. There were also no newly authorised products specifically indicated for the treatment of LGS in the EU.

Amongst the products already authorised in the EU specifically for the treatment of LGS, the only one that has been the subject of clinical trials published since the orphan designation for cannabidiol is rufinamide. Neither of two published studies provides any evidence of an improvement in morbidity or mortality in patients with LGS due to treatment with rufinamide.

Number of people affected or at risk

Mortality rates in patients with LGS have been reviewed to estimate the median survival of patients. Cherian (2017) reported a mortality rate of 7% after a mean follow-up period of 9.7 years. This indicates a survival rate at 9.7 years of 93%. Therefore, the median survival of patients with LGS is in excess of 9.7 years and therefore it is appropriate to use point prevalence to estimate the number of people affected.

Publications identified providing point prevalence data for the EU are discussed below and summarized in Table 1 below.

Table 1:	**Estimated point prevalence for Lennox-Gastaut Syndrome in the EU based on literature reports**			
Source	**Prevalence day**	**Number of cases**	**Study Population/Age group Country**	**Point prevalence (per 10,000)**

Table 1: Estimated point prevalence for Lennox-Gastaut Syndrome in the EU based on literature reports				
Source	**Prevalence day**	**Number of cases**	**Study Population / Age group Country**	**Point prevalence (per 10,000)**
Granieri et al (1983)	31 December 1978	4	45,153 of all ages Italy	0.89
Maremmani et al (1991)	1 December 1985	2	9,952 of all ages Italy	2.01
Sidenvall et al (1996)	31 December 1985	9	53,949 aged 0-16 years Sweden	1.67
Eirksson and Koivikko (1997)	12 December 1992	6	83,464 aged 0-15 years Finland	0.72
Olafsson and Hauser (1999)	1 December 1993	8	89,656 of all ages Iceland	0.89
Waaler et al (2000)	1 January 1995	8	38,593 aged 6-12 years Norway	2.07
Endziniene et al (1997)	1 January 1995	Not stated	< 88,871 aged 0-9 years Lithuania	1.8
Beilmann et al (1999)	31 December 1997	Not stated	157,449 aged 1 month to 19 years Estonia	1
Syvertsen et al (2015)	1 January 2014	9	272,228 of all ages Norway	0.33

The review of point prevalence data for LGS in EU counties shows an occurrence of 0.33-2.01 per 10,000 in the total population. The sponsor discusses the probability that the prevalence would be higher in children. Nevertheless, the COMP accepted the Sponsor's conservative approach, which uses the upper estimate of the prevalence of LGS in the EU. The resulting prevalence of 2 per 10,000 persons is in line with recent orphan designations and the upper limit in publications.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Four products are currently authorised in the EU specifically for the treatment of LGS, namely rufinamide, lamotrigine, topiramate and felbamate, as was the case at the time of the ODA (see Table 2).

Table 2: Summary of Approved Treatment Options for Lennox-Gastaut Syndrome		
Treatment	**Authorisation in the EU**	**Licensed use in LGS (www.medicines.org.uk or EMA Website)**

Table 2: Summary of Approved Treatment Options for Lennox-Gastaut Syndrome		
Treatment	**Authorisation in the EU**	**Licensed use in LGS (www.medicines.org.uk or EMA Website)**
Rufinamide	Approved via the centralised procedure on 16/01/2007	Adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 1 years of age and older.
Lamotrigine	First approval August 1997	Seizures associated with Lennox-Gastaut syndrome.
Topiramate	Nationally approved; Date of first authorisation in UK: 18/07/1995	Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.
Felbamate	Nationally approved: Date of first authorisation in France: 16/05/1994	Adjunctive therapy in the treatment of partial and generalised seizures associated with Lennox-Gastaut syndrome in children. For use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anaemia and/or liver failure is deemed acceptable

Other anti-epileptic drugs may be also considered as satisfactory methods of treatment (such as clobazam and valproate) and are discussed by the sponsor in the context of the current treatment guideline for LGS and in the context of their trials performed for this dossier.

The UK's National Institute for Health and Care Excellence (NICE) have produced a recommended pathway for the treatment of LGS (NICE, 2016). NICE have suggested that first line treatment is sodium valproate. If this is not effective or tolerated then lamotrigine should be prescribed as adjunctive treatment. Other AEDs that may be used are rufinamide, topiramate and felbamate. Usually, it takes a combination of more than one AED to gain any seizure control.

Table 3: Most Common Anti-Epileptic Drugs Used Concomitantly in Pivotal Studies GWEP1423 and GWEP1414 and used in European Clinical Practice to Treat LGS			
Anti-Epileptic Drug	**Study GWEP1423 (N=171)**	**Study GWEP1414 (N=225)**	**European Clinical Practice***
Clobazam	49%	49%	31% (N=75)
Valproic acid	40%	38%	59% (N=75)
Lamotrigine	37%	30%	45% (N=75)
Levetiracetam	34%	31%	29% (N=75)
Topiramate	15%	15%	25% (N=75)
Rufinamide	27%	29%	14% (N=111)
Average number of agents	*3*	*3*	*>1*

* Nikanorova et al (2017). For AEDs other than rufinamide, percentages calculated from Table 1 in the paper by combining data from the "rufinamide" [added] and "no rufinamide" [added] groups. Use of rufinamide calculated as the percentage of 111 patients on rufinamide at study entry.

Significant benefit

Protocol assistance was not sought on demonstrating significant benefit over products specifically authorised in the EU to treat LGS. However, the demonstration of significant benefit had been discussed with the COMP for the clinical programme of cannabidiol in Dravet syndrome, which is another severe, refractory, childhood epilepsy syndrome. In that protocol assistance, the COMP agreed that significant benefit would be established if the pivotal clinical trial showed a superior efficacy of cannabidiol over placebo in patients who were inadequately controlled on the only product specifically authorised in the EU to treat Dravet syndrome, namely stiripentol. The same approach has been used in the LGS programme, although the sub-group of patients analysed was extended to include not only the patients with inadequate control at the time of study entry on each product specifically authorised in the EU to treat LGS, but also those who had previously tried and failed treatment with each of these products.

In the protocol assistance for the Dravet syndrome indication, the COMP also advised that it should be established that any efficacy found in patients inadequately controlled on stiripentol cannot be attributed to a pharmacokinetic interaction with cannabidiol. The same approach has also been used for the LGS indication.

It should be noted that neither of the conducted studies was powered for the presented sub-group analyses, meaning that firm conclusions may not be reliably drawn from each individual sub-group analysis. These post-hoc analyses were not specified in the protocol or statistical analysis plan. Hence the results of a pooled analysis are presented.

Rufinamide

The tables below show the results in patients, who have tried and failed rufinamide, or those who are currently taking it. There is a significantly greater reduction in drop and total seizure frequency and a significantly greater proportion of patients with a ≥ 50% reduction in drop seizure frequency at the 20 mg/kg/day dose of cannabidiol compared with placebo.

Table 4: Percentage Change From Baseline in Drop Seizure Frequency in Patients who are Rufinamide Treatment Failures			
Variable	**Cannabidiol 20 mg/kg/day (N=95)**	**Cannabidiol 10 mg/kg/day (N=47)**	**Placebo (N=95)**
Drop Seizure Frequency (per 28 Days)			
Baseline Period Median (Q1, Q3)	88.00 (35.78, 156.00)	87.61 (44.00, 224.00)	77.47 (47.31, 125.52)
Treatment Period Median (Q1, Q3)	42.30 (16.57, 136.29)	56.00 (23.76, 128.57)	64.84 (34.22, 116.62)
Median % Change During Treatment (Q1, Q3)	−38.78 (−68.53, 1.93)	−32.95 (−60.59, 1.42)	−17.09 (−36.22, 1.06)
Treatment Difference vs. Placebo (95% CI)[a]	−19.34 (−30.75, −7.24)	−9.80 (−23.07, 3.05)	-
P-value[b]	0.0022	0.1314	-

[a] Estimated median difference and 95% CI calculated using the Hodges–Lehmann approach.
[b] p-value calculated from a Wilcoxon rank–sum test.
Source: Annex E, ODD Table 1.1

Table 5: Patients who are Rufinamide Treatment Failures who Achieved At Least a 50% Reduction in Drop Seizure Frequency from Baseline			
Variable	**Cannabidiol 20 mg/kg/day (N=95)**	**Cannabidiol 10 mg/kg/day (N=47)**	**Placebo (N=95)**
≥ 50% Reduction in Drop Seizure Frequency (per 28 Days) from Baseline			
Number of Responders (%)	37 (38.9)	13 (27.7)	16 (16.8)
P-value[a]	0.0011	0.1836	-

[a] p-value calculated from a Fisher's exact test.
Source: Annex E, ODD Table 1.2

Table 6: Percentage Change From Baseline in Total Seizure Frequency in Patients who are Rufinamide Treatment Failures			
Variable	**Cannabidiol 20 mg/kg/day (N=95)**	**Cannabidiol 10 mg/kg/day (N=47)**	**Placebo (N=95)**
Total Seizure Frequency (per 28 Days)			
Baseline Period Median (Q1, Q3)	197.87 (91.72, 408.41)	169.00 (85.00, 517.52)	139.07 (70.48, 446.19)
Treatment Period Median (Q1, Q3)	102.20 (39.32, 289.74)	95.51 (39.26, 223.69)	110.53 (61.14, 326.67)
Median % Change During Treatment (Q1, Q3)	−34.90 (−63.93, −1.44)	−31.25 (−60.71, −10.70)	−12.74 (−37.98, 0.71)
Treatment Difference vs. Placebo (95% CI)[a]	−19.43 (−30.37, −8.55)	−17.54 (−28.27, −5.26)	-
P-value[b]	0.0008	0.0062	-

[a] Estimated median difference and 95% CI calculated using the Hodges–Lehmann approach.
[b] p-value calculated from a Wilcoxon rank–sum test.
Source: Annex E, ODD Table 1.3

Lamotrigine

The tables below show the results in patients, who have tried and failed lamotrigine, and those who are currently taking it. There is a significantly greater reduction in both drop and total seizure frequency and a significantly greater proportion of patients with a ≥ 50% reduction in drop seizure frequency at both doses of cannabidiol compared with placebo.

Table 7: Percentage Change From Baseline in Drop Seizure Frequency in Patients who are Lamotrigine Treatment Failures			
Variable	**Cannabidiol 20 mg/kg/day (N=114)**	**Cannabidiol 10 mg/kg/day (N=49)**	**Placebo (N=116)**
Drop Seizure Frequency (per 28 Days)			
Baseline Period Median (Q1, Q3)	79.59 (32.00, 156.80)	66.71 (31.00, 152.00)	72.84 (43.68, 128.69)
Treatment Period Median (Q1, Q3)	36.30 (15.43, 116.31)	40.29 (13.58, 86.80)	57.99 (33.20, 125.01)
Median % Change During Treatment (Q1, Q3)	−40.74 (−69.62, 3.16)	−37.16 (−62.01, −7.14)	−18.19 (−38.87, 1.01)
Treatment Difference vs. Placebo (95% CI)[a]	−19.24 (−30.07, −7.18)	−18.79 (−30.57, −6.03)	-
P-value[b]	0.0023	0.0040	-

[a] Estimated median difference and 95% CI calculated using the Hodges–Lehmann approach.
[b] p-value calculated from a Wilcoxon rank–sum test.
Source: Annex E, ODD Table 1.1

Table 8: Proportion of Patients who are Lamotrigine Treatment Failures who Achieved At Least a 50 % Reduction in Drop Seizure Frequency from Baseline			
Variable	**Cannabidiol 20 mg/kg/day (N=114)**	**Cannabidiol 10 mg/kg/day (N=49)**	**Placebo (N=116)**
≥ 50% Reduction in Drop Seizure Frequency (per 28 Days) from Baseline			
Number of Responders (%)	47 (41.2)	17 (34.7)	19 (16.4)
P-value[a]	<0.0001	0.0131	-

[a] p-value calculated from a Fisher's exact test.
Source: Annex E, ODD Table 1.2

Table 9: Percentage Change From Baseline in Total Seizure Frequency in Patients who are Lamotrigine Treatment Failures			
Variable	**Cannabidiol 20 mg/kg/day (N=114)**	**Cannabidiol 10 mg/kg/day (N=49)**	**Placebo (N=116)**
Total Seizure Frequency (per 28 Days)			
Baseline Period Median (Q1, Q3)	166.13 (73.00, 404.00)	151.20 (66.71, 314.00)	142.03 (69.56, 427.60)
Treatment Period Median (Q1, Q3)	98.64 (30.89, 266.43)	68.41 (34.42, 179.08)	122.57 (61.89, 366.84)
Median % Change During Treatment (Q1, Q3)	−34.44 (−60.93, −1.44)	−32.87 (−64.77, −3.30)	−14.51 (−39.00, 0.70)
Treatment Difference vs. Placebo (95% CI)[a]	−17.35 (−27.82, −7.42)	−19.63 (−32.11, −6.19)	-
P-value[b]	0.0008	0.0044	-

[a] Estimated median difference and 95% CI calculated using the Hodges–Lehmann approach.
[b] p-value from calculated from a Wilcoxon rank–sum test.
Source: Annex E, ODD Table 1.3

Topiramate

The tables below show the results in patients, who have tried and failed topiramate, and those who are currently taking it. There is a significantly greater reduction in both drop and total seizure frequency at both doses of cannabidiol compared with placebo, and a greater proportion of patients with a ≥ 50% reduction in drop seizure frequency at both doses of cannabidiol compared with placebo (reaching statistical significance for the 20 mg/kg/day dose but only marginal statistical significance for the 10 mg/kg/day dose).

Table 10: Percentage Change From Baseline in Drop Seizure Frequency in Patients who are Topiramate Treatment Failures			
Variable	**Cannabidiol 20 mg/kg/day (N=111)**	**Cannabidiol 10 mg/kg/day (N=56)**	**Placebo (N=122)**
Drop Seizure Frequency (per 28 Days)			
Baseline Period Median (Q1, Q3)	88.00 (37.33, 211.75)	87.95 (42.28, 239.21)	76.87 (46.00, 142.90)
Treatment Period Median (Q1, Q3)	44.00 (17.21, 151.51)	57.02 (23.11, 141.85)	64.95 (33.09, 132.13)
Median % Change During Treatment (Q1, Q3)	−34.13 (−67.28, 4.31)	−36.08 (−60.53, −2.35)	−16.61 (−36.61, 1.06)
Treatment Difference vs. Placebo (95% CI)[a]	−16.83 (−28.28, −4.46)	−16.92 (−28.26, −4.54)	-
P-value[b]	0.0069	0.0074	-

[a] Estimated median difference and 95% CI calculated using the Hodges–Lehmann approach.
[b] p-value calculated from a Wilcoxon rank–sum test.
Source: Annex E, ODD Table 1.1

Table 11: Proportion of Patients who are Topiramate Treatment Failures who Achieved At Least a 50% Reduction in Drop Seizure Frequency from Baseline			
Variable	**Cannabidiol 20 mg/kg/day (N=111)**	**Cannabidiol 10 mg/kg/day (N=56)**	**Placebo (N=122)**
≥ 50% Reduction in Drop Seizure Frequency (per 28 Days) from Baseline			
Number of Responders (%)	40 (36.0)	17 (30.4)	21 (17.2)
P-value[a]	0.0016	0.0517	-

[a] p-value calculated from a Fisher's exact test.
Source: Annex E, ODD Table 1.2

Table 12: Percentage Change From Baseline in Total Seizure Frequency in Patients who are Topiramate Treatment Failures			
Variable	**Cannabidiol 20 mg/kg/day (N=111)**	**Cannabidiol 10 mg/kg/day (N=56)**	**Placebo (N=122)**
Total Seizure Frequency (per 28 Days)			
Baseline Period Median (Q1, Q3)	184.41 (93.00, 470.40)	180.13 (82.65, 494.26)	161.72 (74.06, 402.00)
Treatment Period Median (Q1, Q3)	101.71 (37.53, 322.86)	88.31 (41.06, 206.45)	125.15 (65.05, 349.42)
Median % Change During Treatment (Q1, Q3)	−33.76 (−60.93, −0.09)	−31.57 (−61.30, −6.20)	−14.70 (−39.07, 0.71)
Treatment Difference vs. Placebo (95% CI)[a]	−15.87 (−26.10, −5.32)	−17.04 (−27.40, −5.42)	-
P-value[b]	0.0034	0.0047	-

[a] Estimated median difference and 95% CI calculated using the Hodges–Lehmann approach.
[b] p-value calculated from a Wilcoxon rank–sum test.
Source: Annex E, ODD Table 1.3

Felbamate

The tables below show the results in patients, who have tried and failed felbamate, and those who are currently taking it. There is a greater reduction in drop seizure frequency of marginal statistical significance and a statistically significantly greater proportion of patients with a ≥ 50% reduction in drop seizure frequency at the 20 mg/kg dose of cannabidiol compared with placebo.

Table 13: Percentage Change From Baseline in Drop Seizure Frequency in Patients who are Felbamate Treatment Failures			
Variable	**Cannabidiol 20 mg/kg/day (N=38)**	**Cannabidiol 10 mg/kg/day (N=22)**	**Placebo (N=51)**
Drop Seizure Frequency (per 28 Days)			
Baseline Period Median (Q1, Q3)	81.19 (40.65, 245.00)	130.17 (66.71, 227.86)	76.28 (32.52, 140.00)
Treatment Period Median (Q1, Q3)	47.32 (17.21, 136.29)	68.26 (23.76, 171.39)	58.26 (32.29, 113.79)
Median % Change During Treatment (Q1, Q3)	−31.62 (−74.69, 1.93)	−30.50 (−51.11, 3.03)	−13.64 (−36.06, 2.77)
Treatment Difference vs. Placebo (95% CI)[a]	−17.76 (−36.90, 2.32)	−11.57 (−31.16, 9.21)	-
P-value[b]	0.0930	0.2984	-

[a] Estimated median difference and 95% CI calculated using the Hodges–Lehmann approach.
[b] p-value calculated from a Wilcoxon rank–sum test.
Source: Annex E, ODD Table 1.1

Table 14: Proportion of Patients who are Felbamate Treatment Failures who Achieved At Least a 50% Reduction in Drop Seizure Frequency from Baseline			
Variable	**Cannabidiol 20 mg/kg/day (N=38)**	**Cannabidiol 10 mg/kg/day (N=22)**	**Placebo (N=51)**
≥ 50% Reduction in Drop Seizure Frequency (per 28 Days) from Baseline			
Number of Responders (%)	15 (39.5)	6 (27.3)	7 (13.7)
P-value[a]	0.0068	0.1921	-

[a] p-value calculated from a Fisher's exact test.
Source: Annex E, ODD Table 1.2

Table 15: Percentage Change From Baseline in Total Seizure Frequency in Patients who are Felbamate Treatment Failures			
Variable	**Cannabidiol 20 mg/kg/day (N=38)**	**Cannabidiol 10 mg/kg/day (N=22)**	**Placebo (N=51)**
Total Seizure Frequency (per 28 Days)			
Baseline Period Median (Q1, Q3)	135.07 (63.47, 452.00)	156.89 (89.79, 520.41)	135.00 (68.00, 279.03)
Treatment Period Median (Q1, Q3)	102.20 (31.11, 394.83)	103.09 (38.50, 188.36)	99.14 (60.38, 319.38)
Median % Change During Treatment (Q1, Q3)	−27.56 (−64.07, 7.27)	−34.36 (−64.46, −1.39)	−12.53 (−29.89, −1.61)
Treatment Difference vs. Placebo (95% CI)[a]	−14.58 (−32.78, 4.06)	−21.77 (−40.77, −1.96)	-
P-value[b]	0.1179	0.0282	-

[a] Estimated median difference and 95% CI calculated using the Hodges–Lehmann approach.

[b] p-value calculated from a Wilcoxon rank–sum test.

Source: Annex E, ODD Table 1.3

Furthermore, the sponsor stressed the adverse safety profile of felbamate, which places it into a different risk/benefit category compared with cannabidiol. For example the use of felbamate is associated with a “marked increase in the incidence of aplastic anaemia” and of the risk of acute liver failure, commonly resulting in death or the need for liver transplantation.

Pooled data from two well-controlled, multi-centre, multi-national randomised studies show that patients who are taking, or who have previously taken and have since stopped, the AEDs authorised for use in LGS in the EU, go on to achieve significant benefit from cannabidiol With regards to rufinamide, lamotrigine, topiramate and felbamate it is unlikely that these effects are related to the increased plasma levels of concomitant AEDs due to a pharmacokinetic interaction with cannabidiol, since rufinamide and lamotrigine are metabolised only to a minor degree by cytochrome P450 enzymes (which are inhibited by cannabidiol) (Inovelon 2017; Lamictal, 2017), and no more than 60% of topiramate and felbamate undergo any type of metabolism (Topamax, 2017; Felbatol, 2009). These pooled data analyses show that add-on treatment with cannabidiol is able to provide a clinically relevant advantage over and above that obtained by lamotrigine, rufinamide, felbamate and topiramate. This constitutes a clinically relevant advantage.

The committee relied on the CHMP assessment and the outcome of the scientific advisory group for this marketing authorisation to further understand the interaction of cannabidiol with clobazam and valproate. No statistical differences were observed when evaluating drug-drug interactions with valproate. According to the sponsor approximately 40% of patients received concomitant valproate during the study and many were refractory to this treatment. Therefore, the significant benefit over valproate was accepted.

Some degree of PK interaction between clobazam and cannabidiol was noted. Results of the subgroup analysis of patients treated with clobazam compared to patients treated without clobazam, indicated that there is residual statistical uncertainty regarding the treatment effect of cannabidiol in patients not taking clobazam. In this population, efficacy has not been established. . However, since more than half

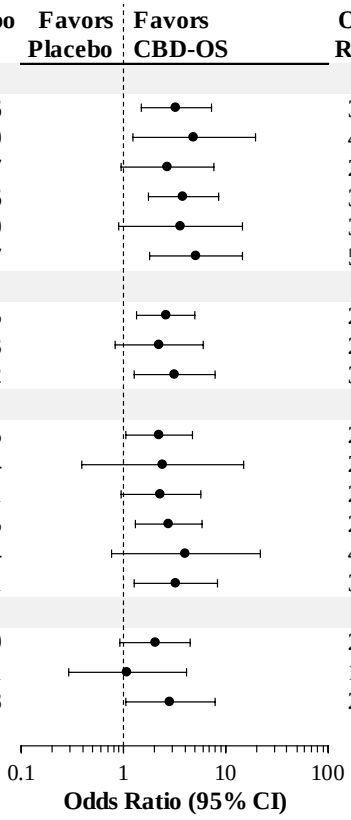
of patients in the studies did receive concomitant clobazam, and the subset analysis showed significant reductions in seizure frequency, the COMP considered significant benefit over clobazam alone justified when these two drugs are taken together (Tables 16 and 17).

Table 16 Baseline Seizure Rate and Prior AED Use in LGS and DS Trials (ITT Analysis Set)

Baseline Characteristics of Patients with LGS or DS	**Taking CLB (N=398)**	**Not Taking CLB (N=316)**
Median number of AEDs used prior to enrolment	5	6
Percentage of patients who failed > 6 AEDs prior to enrolment	29%	43%
Baseline primary seizures/28 days, median	36	54
Baseline total seizures/28 days, median	94	129

Table 17 Logistic regression effect modifier for primary seizure ≥ 50% responders by CLB use

Trial Comparison vs. Placebo	CLB Use	CBD-OS (n/N)	Placebo (n/N)	Odds Ratio (95% CI)	Interaction P-value
GWEP1414 (LGS)					
10 mg/kg/day CBD-OS	All Data	26/73	11/76	3.30 (1.48, 7.35)	
	Off CLB	11/36	3/39	4.92 (1.24, 19.61)	0.5021
	On CLB	15/37	8/37	2.72 (0.96, 7.67)	
20 mg/kg/day CBD-OS	All Data	30/76	11/76	3.87 (1.76, 8.53)	
	Off CLB	10/40	3/39	3.64 (0.91, 14.57)	0.7015
	On CLB	20/36	8/37	5.12 (1.81, 14.54)	
GWEP1423 (LGS)					
20 mg/kg/day CBD-OS	All Data	38/86	20/85	2.61 (1.35, 5.06)	
	Off CLB	15/44	8/43	2.23 (0.83, 6.01)	0.6190
	On CLB	23/42	12/42	3.14 (1.26, 7.81)	
GWEP1424 (DS)					
10 mg/kg/day CBD-OS	All Data	29/66	17/65	2.24 (1.06, 4.73)	
	Off CLB	4/21	2/24	2.42 (0.39, 15.07)	0.9722
	On CLB	25/45	15/41	2.33 (0.96, 5.68)	
20 mg/kg/day CBD-OS	All Data	33/67	17/65	2.77 (1.32, 5.82)	
	Off CLB	8/27	2/24	4.08 (0.76, 22.01)	0.8188
	On CLB	25/40	15/41	3.26 (1.28, 8.26)	
GWEP1332B (DS)					
20 mg/kg/day CBD-OS	All Data	26/61	16/59	2.04 (0.93, 4.51)	
	Off CLB	7/21	7/21	1.09 (0.29, 4.11)	0.2517
	On CLB	19/40	9/38	2.88 (1.06, 7.84)	



In light of the narrower therapeutic indication which will only allow the use of cannabidiol in conjunction with clobazam, the COMP considered that the data in support of significant benefit in this setting is sufficient. The COMP considered that further reduction of seizures when added to the current standard of care constitutes a clinically relevant advantage and confirms the assumptions made at the time of initial orphan designation.

2.4. COMP position adopted on 26 July 2019

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated orphan medicinal product;
- the prevalence of Lennox-Gastaut syndrome (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;

- the condition is chronically debilitating due to the high frequency of multiple types of seizures, cognitive deterioration, behavioural disturbances, and poor long term prognosis despite existing treatments and life threatening due to a risk of sudden unexpected death due to epilepsy;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Epidyolex may be of potential significant benefit still holds. The sponsor provided clinical evidence to demonstrate that Epidyolex in conjunction with clobazam reduced seizure frequency in patients who have not adequately responded to clobazam or other authorised products for this condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Epidyloex (cannabidiol), EU/3/17/1855 for treatment of Lennox-Gastaut syndrome is not removed from the Community Register of Orphan Medicinal Products.

3. Epidyloex (cannabidiol) for treatment of Dravet syndrome EU/3/14/1339 (EMA/OD/083/14)

3.1. Product and administrative information

Product	
Active substance	Cannabidiol
International Non-Proprietary Name	Cannabidiol
Orphan condition	Treatment of Dravet syndrome
Pharmaceutical form	Oral solution
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	Antiepileptics, other antiepileptics (N03AX)
Sponsor's details:	GW Pharma (International) B.V. Databankweg 26 Amersfoort 3821 AL Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	GW Pharma Ltd
COMP opinion date	4 September 2014
EC decision date	15 October 2014
EC registration number	EU/3/14/1339
Post-designation procedural history	
Transfer of sponsorship	- Transfer from GW Pharma Ltd to GW Research Ltd – EC decision of 16 November 2017 - 2nd transfer from GW Research Ltd to GW Pharma (International) B.V – EC decision of 10 April 2019
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	M. Ainsworth, O. Slanař
Applicant	GW Pharma (International) B.V.
Application submission date	21 December 2017
Procedure start date	1 February 2018
Procedure number	EMEA/H/C/004675
Invented name	Epidyolex
Therapeutic indication	Epidyolex is indicated for 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 Further information on Epidyolex can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex
CHMP opinion date	25 July 2018
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	D. Duarte, G. Capovilla

Sponsor's report submission date	18 September 2018
COMP opinion date (adoption via written procedure)	26 July 2019

3.2. Grounds for the COMP opinion at the designation stage

The sponsor GW Pharma Ltd submitted on 15 May 2014 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing cannabidiol for treatment of Dravet syndrome (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing cannabidiol was considered justified based on preliminary clinical data in patients with the condition;
- the condition is chronically debilitating due to psychomotor and cognitive impairment and the occurrence of convulsive seizures, and life-threatening in particular due to generalized tonic-clonic seizures;
- the condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cannabidiol may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that when used in combination with anticonvulsants there was a clinically relevant reduction in seizures associated with the condition. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing cannabidiol, as an orphan medicinal product for the orphan indication: treatment of Dravet syndrome.

3.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor reported that the International League Against Epilepsy (ILAE) issued a revised classification of seizure and epilepsy types in March 2017. This did not alter the classification of epilepsy syndromes (Scheffer et al, 2017). Therefore, Dravet Syndrome remains a recognised

electroclinical epilepsy syndrome in accordance with the 2010 ILAE classification system (Berg et al, 2010).

Dravet syndrome (DS) is one of the most severe genetic epilepsy, which is predominantly caused by (usually de novo) heterozygous mutations in the SCN1A gene encoding a voltage-gated sodium channel. DS is characterised by the onset of febrile or afebrile convulsive seizures (clonic or hemiclonic) usually in the first year of life, evolving into status epilepticus in infants with initially normal psychomotor development. Subsequently, the clinical epileptic scenario is complicated by the appearance of pharmaco-resistant photo- or pattern-induced seizures, myoclonic seizures, atypical absences until obtundation status, as well as complex partial seizures (Bureau and Dalla Bernardina, 2011). Moreover, cognitive impairment and neurological signs with motor disorders of various degrees appear over the years.

The approved therapeutic indication Epidyolex is indicated for 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 falls within the scope of the designated orphan indication “Dravet Syndrome” in combination with another orphan drug designation held by the sponsor for the “treatment of Lennox-Gastaut syndrome”.

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified (please also see Epidyolex EPAR).

The clinical development program supporting the efficacy of CBD-OS comprises 2 randomised, placebo-controlled trials in DS; 1 investigating 10 and 20 mg/kg/day CBD-OS (GWEP1424) and 1 investigating 20 mg/kg/day CBD-OS (GWEP1332 Part B).

The pivotal trial consisted of a 4-week baseline period, followed by a 14-week treatment period comprising a 2-week titration (dose escalation) period and a 12-week maintenance (stable dosing) period. Patients who discontinued the investigational medicinal product (IMP) were to taper the dose over a 10-day period, with a safety follow-up 4 weeks after final dose.

Primary and key secondary endpoints centred primarily on changes in seizure frequency, and were based on daily seizure reports. The number and type of seizures experienced by a patient were reported daily using a telephone-based IVRS. The primary endpoint was the percentage change from baseline in convulsive seizure frequency during the treatment period, for CBD-OS compared with placebo. The pivotal trials included as a key secondary endpoint the proportion of CBD-OS vs. placebo patients who achieved at least a 50% reduction from baseline in convulsive seizure frequency. Other key secondary endpoints in the trials included the percentage change from baseline in total seizure frequency during the treatment period, and the Subject/Caregiver Global Impression of Change (S/CGIC) at last visit, for CBD-OS compared with placebo.

Study GWEP1332B: The median percentage change from baseline in total convulsive seizure frequency during the treatment period was −38.94 in the CBD-OS group compared with −13.29 in the placebo group. The estimated median difference was in favour of CBD-OS treatment over placebo (−22.79; 95% CI: −41.06, −5.43) and the difference between treatments was statistically significant (p=0.0123).

Study GWEP1424: The median percentage change from baseline in total convulsive seizure frequency during the treatment period was -48.7 in the 10 mg/kg/day CBD-OS group, -45.7 in the 20 mg/kg/day CBD-OS group, and -26.9 in the placebo group. The estimated median difference was in favour of CBD-OS treatment over placebo for both 10 mg/kg/day CBD-OS and 20 mg/kg/day CBD-OS; the

difference between each CBD-OS group and placebo was statistically significant (p=0.0095 and p=0.0299, respectively).

Similar degrees of reduction were seen in total seizures as well as across seizure types.

CBD-OS can cause hepatocellular injury. Two patients concomitantly treated with valproate experienced toxic hepatocellular injury in combination with metabolic acidosis and encephalopathy, respectively. The incidence of TEAEs meeting the search criteria for AESI abnormal liver TEAEs was 14.9% in the All CBD-OS group (N=456) compared with 3.1% in the placebo group (N=292). However, the number of liver-related adverse events was strongly dose-dependent.

Currently available antiepileptic treatment rarely succeeds in keeping the children free of seizures and the risk of sudden unexpected death in epilepsy (SUDEP) remains high. In that respect, the statistically significant reduction in seizure frequency offered by CBD-OS constitutes a favourable effect in this difficult to treat population. A reduction of 50% in the frequency of seizures is considered a clinically relevant effect. However, some notable uncertainties about the favourable effect of CBD-OS remain. Results of the subgroup analysis of patients treated with clobazam compared to patients treated without clobazam, indicated that there is residual statistical uncertainty regarding the treatment effect of cannabidiol in patients not taking clobazam. In this population, efficacy has not been established. Therefore, the indication proposed by the CHMP was narrower than originally proposed by the sponsor.

Chronically debilitating and/or life-threatening nature

There is no evidence that the level of disability and mortality with Dravet syndrome has changed significantly since the time of the orphan designation. This is supported by a recent review on long-term outcomes in patients with Dravet syndrome (Connolly, 2016). Since the initial orphan drug designation, only one clinical non-randomised study has been published that investigated the efficacy and safety of stiripentol in treating Dravet syndrome. This was a study of the use of stiripentol for up to 40 weeks in treating 24 Japanese patients who were inadequately controlled on clobazam and/or valproate. Of the 19 patients completing the study, 54% had a ≥50% reduction in the frequency of clonic/tonic-clonic seizures compared with baseline. However, the effect of treatment on disability or mortality was not investigated. Therefore, there is no evidence that any treatment for Dravet syndrome has improved the disability or mortality caused by the condition since the orphan designation. The condition remains a chronically debilitating and life threatening in nature.

Number of people affected or at risk

Based on literature review and for the purpose of prevalence calculation the sponsor made a few assumptions:

1) A literature review indicates a survival rate at 9.25 years of at least 84%. Therefore, the median survival of patients with Dravet syndrome is in excess of 9-10 years. It is appropriate to use 10-years partial prevalence to estimate the number of people affected.

2) This search identified only two reports on the prevalence of Dravet Syndrome in the EU; one from Sweden (Rosander & Hallböök, 2015) and another from Norway (Syvertsen et al, 2015).

Based on these studies the point prevalence of Dravet syndrome in the EU is approximately 0.11 people per 10,000 total population, and possibly as high as 0.3 per 10,000. This is less than the value of < 0.5 per 10,000 given at orphan designation and also given for two other products with orphan designations in Dravet syndrome, and is less than the EMA's estimate of 0.4 per 10,000 (EMA/452415/2012 Rev 1), but similar to the birth prevalence of Dravet syndrome of 0.25 per 10,000 cited by Orphanet (2018). Therefore, the Sponsor continues to agree that the estimate of the

prevalence of Dravet syndrome in the EU is less than 0.5 per 10,000 persons. The COMP considered that this estimate is acceptable.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

At this time, the only product authorised in the EU specifically for the treatment of Dravet syndrome remains Diacomit (stiripentol), as was the case at the time of the ODA.

In addition, (sodium) valproate and clobazam, although not formally authorised for this condition, are recommended in Dravet syndrome and may therefore be considered as a satisfactory method of treatment.

In 2015, a working party of the ILAE, which included participants from EU countries (Belgium, France, Italy, Romania and UK), published guidelines on the management of infantile seizures, including Dravet syndrome (Wilmshurst et al, 2015). These guidelines, based on systematic reviews of the literature, concluded that stiripentol (in combination with clobazam and valproate) is the only therapy for which there is strong evidence of efficacy in Dravet syndrome. The sponsor included a table comparing the drugs commonly used in European standard of care as compared to the study supporting this dossier (Table 1).

Table 1: Most Common Anti-Epileptic Drugs Used Concomitantly in Part B of Study GWEP1332 and Used in European Clinical Practice to Treat Dravet Syndrome

Anti-Epileptic Drug	GWEP1332B (N=120)	European Clinical Practice* (N=274)
Clobazam	65%	55%
Valproate	57%	86%
Stiripentol	42.5%	42%
Levetiracetam	27.5%	22%
Topiramate	26%	44%
Average number of agents	*3*	*3*

Significant benefit

Protocol assistance was provided in June 2015 on demonstrating significant benefit over stiripentol using data from the clinical trials programme. In protocol assistance provided in June 2015, the COMP stated that "if patients with Dravet Syndrome insufficiently controlled by currently authorised antiepileptic treatments become seizure free, and/or experience a significant reduction in the number of seizures, under treatment with cannabidiol, this would constitute a clinically relevant advantage."

Further:

"Since significant benefit needs to be demonstrated over stiripentol, it is strongly recommended that a sufficient number of patients treated with stiripentol should be included in both arms."

And:

"Furthermore, a drug-drug interaction study, looking at the effect of cannabidiol on the pharmacokinetics of stiripentol will clarify whether cannabidiol affects exposure to stiripentol."

The sponsor addressed these comments by the COMP in the following:

With regards to efficacy, amongst 120 patients in study GWEP1332 Part B (mean age 9.8 years) on at least one concomitant AED (median of 3) randomised to double-blind treatment with placebo or cannabidiol (titrated to 20 mg/kg/day) for 14 weeks, the primary efficacy variable (percentage change from baseline in total convulsive seizure frequency during the treatment period) was statistically significantly greater with cannabidiol than placebo (median difference -22.79% [95% CI: -41.06, -5.43]; p=0.0123, ITT analysis). Sensitivity and subgroup analyses were consistent with this result. The proportion of patients with a ≥ 50% reduction in baseline convulsive seizure frequency during treatment (a key secondary efficacy variable) was greater in the cannabidiol than the placebo group (43% vs 27%, respectively, ITT analysis). The odds ratio (2.00; 95% CI: 0.93, 4.30) was in favour of cannabidiol over placebo; this result approached, but fell short of, statistical significance (p=0.0784).

With regards to stiripentol, amongst the 51 patients receiving concomitant stiripentol, the percentage change from baseline in total convulsive seizure frequency during the treatment period (the primary efficacy variable) was statistically significantly greater with cannabidiol (N=30) than placebo (N=21) (median difference -32.70% [95% CI: -57.12, -9.01], p=0.0085, ITT analysis). Consistent with this result, the proportion of patients with a ≥ 50% reduction in baseline convulsive seizure frequency during treatment was numerically greater with cannabidiol than placebo amongst the patients receiving concomitant stiripentol (30.0 vs 9.5%, respectively; p=0.0977).

Since stiripentol is authorised only in combination with valproate and clobazam, the committee assumed all patients on stiripentol would also receive valproate. No statistical differences were observed when evaluating drug-drug interactions with valproate in a non-clinical model. According to the sponsor approximately 57% of patients received concomitant valproate during the study (more than the proportion of patients receiving stiripentol) and many were refractory to this treatment. Therefore, the significant benefit over valproate was accepted.

The drug-drug interactions were investigated in pharmacokinetic study GWEP1543 in 12 healthy subjects. The study was designed to demonstrate maximum effects of cannabidiol on stiripentol exposure under highly controlled conditions. At steady state, cannabidiol increased the maximum plasma concentration (Cmax) of stiripentol by 28% (95% CI: 8-52%) and the area under the plasma concentration-time curve over the dosing interval (AUCtau) by 55% (95% CI: 42-69%). However, this effect was not considered clinically significant since the upper limits of the 95% confidence intervals did not exceed 2. However, interactions with clobazam, another drug used in DS, have been discussed by the CHMP and confirmed by the sponsor. In addition, the subgroup analysis indicated that there is residual statistical uncertainty regarding the treatment effect of cannabidiol in patients not taking clobazam. These doubts led to the exclusion of the population not taking concomitant clobazam by the CHMP. The COMP further discussed what proportion of patient in the studies used clobazam and whether combined effects of stiripentol and clobazam together, elevated by the cannabidiol-mediated cyp450 inhibition, could contribute to the therapeutic effects observed. It will be of interest to elucidate the effects of CBD on its own and the mechanism of this effect. However, in light of the narrower therapeutic indication which will only indicate the use of CBD in combination with clobazam, the COMP considered that the data in support of significant benefit in this setting is sufficient. The COMP considered that further reduction of seizures when added to the current standard of care constitutes a clinically relevant advantage and confirms the assumptions made at the time of initial orphan designation.

3.4. COMP position adopted on 26 July 2019

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated orphan medicinal product,
- the prevalence of Dravet syndrome (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to psychomotor and cognitive impairment and the occurrence of multiple types of epileptic seizures, and life-threatening due to status epilepticus and sudden unexpected death due to epilepsy;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Epidyolex may be of potential significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication still holds. The sponsor provided clinical evidence to demonstrate that Epidyolex in conjunction with clobazam reduced seizure frequency in patients who have not adequately responded to the combination of clobazam, stiripentol and sodium valproate.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Epidyloex (cannabidiol), EU/3/14/1339 for treatment of Dravet syndrome is not removed from the Community Register of Orphan Medicinal Products.