16 April 2021
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Epidyolex (cannabidiol)
Treatment of tuberous sclerosis
EU/3/17/1959
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. Product and administrative information

Product	
Designated active substance(s)	Cannabidiol
Other name(s)	-
International Non-Proprietary Name	Cannabidiol
Tradename	Epidyolex®
Orphan condition	Treatment of tuberous sclerosis
Sponsor's details:	GW Pharma (International) B.V. Databankweg 26 3821 AL Amersfoort Utrecht Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	GW Research Ltd
COMP opinion date	7 December 2017
EC decision date	17 January 2018
EC registration number	EU/3/17/1959
Post-designation procedural history	
Transfer of sponsorship	Transfer from GW Research Ltd to GW Pharma (International) B.V. – EC decision of 10 April 2019
Type II variation procedural history	
Rapporteur / Co-rapporteur	H. L. Larsen / O. Slanař
Applicant	GW Pharma (International) B.V.
Application submission date	19 March 2020
Procedure start date	25 April 2020
Procedure number	EMEA/H/C/004675/II/0005
Invented name	Epidyolex
Proposed therapeutic indication	For use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 year 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 February 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	E. J. Rook / D. Duarte
Sponsor's report submission	13 May 2020
COMP discussion and adoption of list of questions	19-21 January 2021
Oral explanation	16 March 2021
COMP opinion	18 March 2021

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

The sponsor GW Research Ltd submitted on 31 August 2017 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing cannabidiol for treatment of tuberous sclerosis (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 showing a reduction in seizure frequency in patients with the condition;
- the condition is chronically debilitating due to facial disfigurement and severe neurological symptoms and life threatening due to the formation of multiple tumours;
- the condition was estimated to be affecting approximately 1 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 preliminary clinical data demonstrating a relevant reduction in seizure frequency in patients refractory to anticonvulsant therapy. 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: for treatment of tuberous sclerosis.

3. Review of criteria for orphan designation at the time of type II variation

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

Tuberous sclerosis or tuberous sclerosis complex TSC is an autosomal dominant inherited neurocutaneous disorder that is characterised by the development of multiorgan benign tumour-like growths, most usually observed in the skin, brain, kidney, heart and lungs that could potentially lead to organ dysfunction.

TSC is caused by mutations in two genes: TSC1 gene is located on chromosome 9 and produces a protein called hamartin. The TSC2 gene is located on chromosome 16 and produces the protein tuberin. These two proteins create a complex that regulates the mammalian target of rapamycin (mTOR).

Due to the pathophysiology of TSC, the progression and appearance of its signs and symptoms are slow and subtle thus, patients are usually misdiagnosed or diagnosed at later stages in life. Focal cortical malformations (FCMs) are the most common cause of medically intractable epilepsy (resistant to antiepileptic drug polytherapy) in the paediatric patient population.

The definition and description of the condition has not changed since the initial orphan designation.

The approved therapeutic indication "For use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 year of age and older" falls within the scope of the designated orphan condition "treatment of tuberous sclerosis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by a positive benefit/risk assessment of the CHMP (see EPAR).

Chronically debilitating and/or life-threatening nature

No additional medicines have been approved specifically for the treatment of tuberous sclerosis since the initial orphan drug designation application was approved in January 2018.

Tumours in TSC patients can occur in any major organ, and they develop primarily in the brain, eyes, heart, kidney, skin, and lungs (Crino 2006). Whereas SENs and SEGAs are usually asymptomatic, the presence of cortical tubers is widely believed to contribute to the neurologic manifestations of TSC, which include epilepsy, cognitive disability, and autism (Crino 2006; Curatolo 2008; Northrup 2013).

Morbidity and mortality are increased in TSC patients with treatment-resistant epilepsy (Chu Shore 2010). Sudden unexplained death in epilepsy (SUDEP) was the second most common cause of death after TSC kidney disease in a study of all patients with TSC (Amin 2017). Analysis of epilepsy studies have identified frequent generalized seizures as a major risk factor for SUDEP (Hesdorffer 2011; Ryvlin 2013). Therefore, a critical therapeutic goal in treatment of TSC is decreasing seizures.

The condition remains chronically debilitating and life threatening.

Number of people affected or at risk

Based on the references found in updated literature search, the estimated prevalence of TSC in the EU ranges from 0.1 to 0.9 per 10,000 persons, as summarised in Table 1.

Table 1. Summary of Published Estimates of Prevalence of TSC Within the EU

Author	Prevalence reported in publication	Estimated prevalence per 10,000 persons
Hunt (1984)	1 in 34,200	0.3
Sampson (1989)	1 per 27,000	0.4
Osborne (1991)	1 per 34,107	0.3
Webb (1996)	1 per 26,500	0.4
O'Callaghan (1998)	8.8 per 100,000	0.9
Devlin (2006)	1 per 24,956	0.4
Kingswood (2016)	-	0.1

Using a mean of the above figures, an estimated prevalence of TSC in the EU is 0.4 per 10,000 persons. The range of values provided above, and the estimate given at the time of initial designation would support adoption of 'less than 1 in 10,000' value in this case. The estimate and the range of values submitted by the sponsor are 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

TSC associated seizures can be treated with several anti-seizure medicines, including vigabatrin, corticotropin (ACTH) or steroids, lamotrigine, levetiracetam, carbamazepine, felbamate, clobazam etc, their use depending on the type of seizures and epileptic syndrome. A significant proportion of patients (37–63%) become resistant to treatment with these medicines (Chu-Shore 2010; Vignoli 2013; French 2016).

Everolimus is the only therapy specifically authorised for adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with TSC.

Everolimus (the 40-O-[2-hydroxyethyl] derivative of sirolimus/rapamycin) is a kinase inhibitor that selectively inhibits mTOR activity (Votubia 2020).

Significant benefit

Despite the availability of everolimus, a large number of patients with TSC experience refractory seizures. Only 3.8% to 5.1% of patients with TSC associated seizures were seizure free during everolimus treatment compared with 0.8% in the placebo group in the everolimus phase 3 study

EXIST 3; 50% or greater reduction in seizure frequency from baseline was achieved by 28% to 40% of patients who were treated with everolimus compared with 15% of patients treated with placebo. (French 2016).

At the time of initiation of the GWEP1521 trial in April 2016, no drugs were specifically approved for the treatment of TSC-associated seizures. Therefore, Protocol Assistance has not been sought in the EU regarding the demonstration of significant benefit specifically to treat TSC.

The sponsor proposed that CBD-OS offers improved efficacy when used as adjunctive treatment with currently used AEDs and a major contribution to patient care over everolimus.

Trial GWEP1521 enrolled patients aged 1 to < 57 years of age, with a clinical diagnosis of TSC and a documented history of epilepsy not completely controlled by 1 or more current AEDs. The majority of the patient population was male (58%), White/Caucasian (90%), and < 18 years of age (74%). The median number of current AEDs was 3 (range: 0–5), with the most common being valproic acid (45%), vigabatrin (33%), levetiracetam (29%), and clobazam (27%).

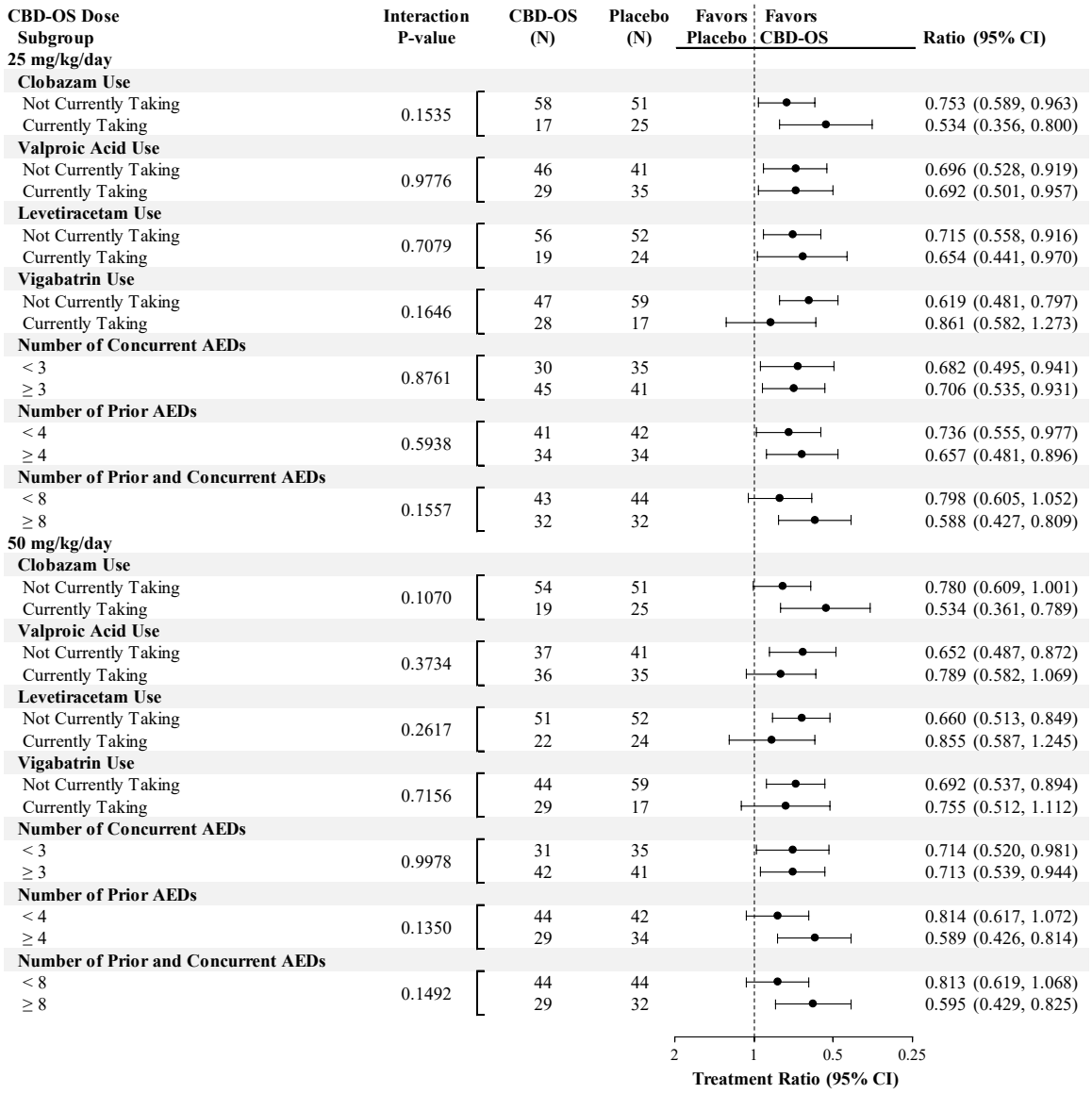
The patient population had failed a median 4 AEDs prior to treatment, most commonly levetiracetam (53%) and vigabatrin (49%). Eligibility based on seizure count was confirmed at the end of the 4-week baseline period. The most common current seizure types reported during baseline period were Type 2 focal (focal seizures with impairment of consciousness or awareness) (67.0% of all patients); Type 3 focal (focal seizures evolving to bilateral generalized convulsive seizures) and tonic seizures (both 29% of all patients), tonic-clonic (23% of all patients) and atonic (12.5% of all patients). The median TSC-associated seizure frequency (average per 28 days) during this time was 57 (range: 8 to 558), or a median of 2 seizures per day.

Table 2. Negative Binomial Regression Analysis of TSC associated Seizure Count During Baseline and Treatment Periods (GWEP1521 ITT Analysis Set)

Variable **Statistics**	**CBD-OS** **25 mg/kg** **(N=75)**	**CBD-OS** **50 mg/kg** **(N=73)**	**Placebo** **(N=76)**
Estimated Mean Seizure Rate per 28 Days			
Baseline Period	51.6	66.3	54.8
95% CI	(40.8, 65.3)	(52.3, 84.2)	(43.4, 69.3)
Treatment Period	26.5	34.9	40.3
95% CI	(21.0, 33.5)	(27.5, 44.2)	(31.9, 50.8)
Estimated Ratio [Percentage Reduction]			
Treatment Period/Baseline Period	0.514 [48.6%]	0.525 [47.5%]	0.735 [26.5%]
95% CI	(0.442, 0.596) [40.4%, 55.8%]	(0.452, 0.610) [39.0%, 54.8%]	(0.635, 0.851) [14.9%, 36.5%]

CBDOS = cannabidiol oral solution; CI = confidence interval; ITT = intention to treat; TSC = tuberous sclerosis complex.
Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.
Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.
Note: Model includes total number of seizures as a response variable, age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

Figure 1. Negative Binomial Regression Effect Modification Analysis of TSC associated Seizure Count During Baseline and Treatment Periods in TSC Trial GWEP1521 Double-blind Phase for Use of Antiepileptic Drugs (ITT Analysis Set)



AED = antiepileptic drug; CBD OS = cannabidiol oral solution; CI = confidence interval; ITT = intention to treat; TSC = tuberous sclerosis complex.
Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.
Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.
Note: The placebo arms were pooled for the analysis of efficacy.
Note: Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction, and factor by time by treatment interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

The benefit of Epidyolex as an adjunctive treatment to the standard anti-epileptic treatments was demonstrated by the positive benefit risk assessment in this setting. The benefit of Epidyolex has been shown for those patients who were failing on prior treatments with vigabatrin, valproic acid or levetiracetam. This comparison to standard anti-seizure medicines was accepted.

In the initial sponsor's position Epidyolex treatment in TSC patients constitutes a major contribution to patient care compared with everolimus. The analysis of significant benefit over everolimus is of most relevance for the discussion of significant benefit because of closely overlapping indications.

The arguments to support the significant benefit versus everolimus were proposed as follows:

1. Different mechanism of action. This argument is not sufficient on its own because it also has to translate to relevant changes in efficacy or safety of the product. However, the fact that Epidyolex acts through a different mechanism of action may be used as an explanation of the claimed clinically relevant advantage.

2. Fulfilment of an unmet need: despite the availability of everolimus, a large number of patients with TSC experience refractory seizures. Only 3.8% to 5.1% of patients with TSC associated seizures were seizure free during everolimus treatment compared with 0.8% in the placebo group in the everolimus phase 3 study EXIST3; 50% or greater reduction in seizure frequency from baseline was achieved by 28% to 40% of patients who were treated with everolimus compared with 15% of patients treated with placebo (French 2016). This argument can only be used if Epidyolex is shown to fulfil this unmet need. In the absence of a comparative trial or date in everolimus refractory population, this is not possible to assess.

3. Improved efficacy was claimed based on the fact that Epidyolex is indicated for a broader patient population. While efficacy regarding focal-onset seizure reduction is on par with everolimus (historic control) in comparable refractory study populations, Epidyolex is indicated for a broader target population including also generalised-onset seizures, and a high response was confirmed in this special patients' group. In contrast, in the SmPC of Votubia it is mentioned that the use of this drug has not been established in patients with generalised-onset seizures. The COMP questioned the true existence of the generalised-onset seizures in the TSC population, because it is believed that all seizures in these patients are of focal origin. However, in discussion with the sponsor it was acknowledged that in approximately 10% of patients it is not possible to differentiate between focal and generalised seizures. Patients affected by such seizures were actively excluded in the EXIST-3 study, whereas in GWEP1521 they were included and significant efficacy in this patient population was observed.

4. Safety profile is claimed to be favourable for Epidyolex, with a considerably lower number of Important Identified Risks than established for Votubia in the Risk Management Plans. Main safety issues with cannabidiol are somnolence and weight loss, and usually reversible liver function disorders (ALT/AST increments). In contrast, Votubia is a narrow-therapeutic window drug which requires regular monitoring of the drug plasma level as it can be nephrotoxic at higher dose levels, and cause myelosuppression (neutropenia, lymphopenia, anaemia, and thrombocytopenia) - and consequently, serious infections. This argument was questioned by the COMP, especially in context of a potential combination therapy of Epidyolex and Votubia. However, the sponsor explained that many patients will never receive Votubia due to associated safety concerns and patients unable to tolerate long-term treatment with Votubia would benefit from treatment with Epidyolex. This argument was accepted. Furthermore, Votubia is prone to pharmacokinetic interactions with CYP3A4 inhibitors, whereas this is not the case for Epidyolex. This argument was acknowledged and not discussed further.

5. Major contribution to patient care is claimed based on the fact that regular monitoring is required during the use of Votubia regarding drug plasma level and safety parameters (haematology, lipids and renal function). This is in contrast to CBD where less monitoring is required (liver enzymes

only). However, no quantification of treatment burden was presented, and it was not supported by adequate patient reported outcomes. Thus, the COMP considered this argument as invalid.

Taken together, the Committee agreed that the claim of significant benefit of Epidyolex over Votubia holds based on clinically relevant advantage. Both, efficacy and safety arguments were considered valid.

4. COMP position adopted on 18 March 2021

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 tuberous sclerosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be less than 1 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 disfiguring tumours and severe neurological symptoms including treatment-resistant seizures that can lead to cognitive disability and life threatening due to the formation of multiple tumours;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Epidyolex may be of potential significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. Epidyolex is authorised for a broader range of seizures, whereas Votubia is authorised only in partial-onset seizures with or without secondary generalisation in tuberous sclerosis. Furthermore, the safety profile of Epidyolex is considered significantly different to that of Votubia. In contrast to Votubia, Epidyolex is not associated with immunosuppression, which offers an alternative for patients who cannot tolerate the chronic use of Votubia. These arguments constitute a clinically relevant advantage.

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 Epidyolex, cannabidiol, for treatment of tuberous sclerosis (EU/3/17/1959) is not removed from the Community Register of Orphan Medicinal Products.