26 April 2023
EMA/CHMP/254054/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Epidyolex

International non-proprietary name: cannabidiol

Procedure No. EMEA/H/C/004675/II/0020

Note

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

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List of abbreviations

Abbreviation	Definition/Explanation
7-OH-CBD	7-hydroxy-cannabidiol
A1	Adenosine receptor type A1
A2A	Adenosine receptor type 2A
AE	Adverse event
AELD	Adverse event leading to discontinuation
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASM	Antiseizure medication (former terminology used antiepileptic drug [AED])
AUC	Area under the concentration-time curve
CBD	Cannabidiol
CBD-OS	Cannabidiol oral solution
CDF	Cumulative distribution function
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLB	Clobazam
Cmax	Maximum measured plasma concentration
COMP	Committee for Orphan Medicinal Products
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DS	Dravet syndrome
ENT-1	Equilibrative nucleoside transporter-1
FDA	Food and Drug Administration
GPR55	G-protein coupled receptor 55
IMP	Investigational medicinal product
ITT	Intention to treat
IVRS	Interactive voice response system
LGS	Lennox–Gastaut syndrome
MAA	Marketing Authorization Application
MOA	Mechanism of action
N-CLB	N-desmethylclobazam (the active metabolite of CLB)

NDA	New Drug Application
OLE	Open-label extension
OR	Odds ratio
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QoL	Quality of life
RCT	Randomized controlled trial
SAE	Serious adverse event
SAG	Scientific Advisory Group
STP	Stiripentol
SmPC	Summary of product characteristics
sNDA	supplemental New Drug Application
SUDEP	Sudden unexpected death in epilepsy
TIIV	Type II variation
TRPV1	Transient receptor potential vanilloid 1
TSC	Tuberous sclerosis complex
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GW Pharma (International) B.V. submitted to the European Medicines Agency on 9 March 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment with Epidyolex as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) for patients 2 years of age and older (without the restriction for use only in conjunction with clobazam), based on the previously generated data in patients treated without CLB in the LGS and DS pivotal studies re-evaluated in the context of the more recent evidence from study GWEP1521 in tuberous sclerosis complex (TSC). As a consequence, sections 4.1, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement editorial changes in the product information. Version 2.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

However, during the procedure and in view of the CHMP data assessment, the marketing authorisation holder revised the scope the variation and instead of the extension of the indication, proposed the update of section 4.8 of the SmPC to provide further details regarding the increased risk of pneumonia as well as section 5.1 of the SmPC to reflect the outcome of the P46 011.1 procedure, as concluded in January 2023.

Information relating to orphan designation

EU/3/14/1339 on 15/10/2014 and EU/3/17/1855 on 20/03/2017. Epidyolex was designated as an orphan medicinal product in the following indications: 'Treatment of Dravet syndrome' and 'Treatment of Lennox-Gastaut syndrome', respectively.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0033/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001964-PIP01-16-M03 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Ondřej Slanař

Timetable	Actual dates
Submission date	09 March 2022
Start of procedure:	18 June 2022
CHMP Rapporteur Assessment Report	12 August 2022
PRAC Rapporteur Assessment Report	12 August 2022
CHMP Co-Rapporteur Assessment	24 August 2022
Updated PRAC Rapporteur Assessment Report	25 August 2022
PRAC Outcome	01 September 2022
CHMP members comments	05 September 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	08 September 2022
1st Request for supplementary information (RSI)	15 September 2022
Submission of MAH's responses to 1st RSI	15 November 2022
CHMP Rapporteur Assessment Report	29 November 2022
CHMP members comments	06 December 2022
Updated CHMP Rapporteur Assessment Report	09 December 2022
2nd Request for supplementary information (RSI)	15 December 2022
Submission of MAH's responses to 2nd RSI	27 January 2022
CHMP Rapporteur Assessment Report	07 March 2023
CHMP members comments	17 March 2023
Updated CHMP Rapporteur Assessment Report	24 March 2023
An Oral Explanation took place on	28 March 2023
3rd Request for supplementary information (RSI)	30 March 2023

Timetable	Actual dates
Submission of MAH's responses to 3rd RSI	03 April 2023
CHMP Rapporteur Assessment Report	12 April 2023
CHMP members comments	17 April 2023
Updated CHMP Rapporteur Assessment Report	20 April 2023
Opinion	26 April 2023
The CHMP adopted a report on similarity of Epidyolex with Fintepla (see Appendix 1)	26 April 2023

2. Scientific discussion

2.1. Introduction

The original Marketing Authorisation for Epidyolex, cannabidiol oral solution (CBD-OS), was granted in EU on 19 September 2019, for use as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, in patients 2 years of age and older.

In April 2021, Epidyolex was also approved as an adjunctive treatment of seizures associated with Tuberous Sclerosis Complex (TSC), for patients 2 years of age and older (without restriction to any co-medications (extension of indication EMEA/H/C/004675/II/0005)).

In this application, the MAH proposes to update the Epidyolex indication for the use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) for patients 2 years of age and older, without the restriction for use only in conjunction with clobazam.

In order to support the proposed extension of indication and demonstrate the independent efficacy of CBD-OS, without CLB, in LGS and DS patients, the MAH referred to existing *in-vivo* non-clinical data, which demonstrate the anticonvulsive activity of CBD-OS and its metabolites, and clinical data in patients treated with CBD-OS without CLB. The summary of clinical data includes results of subgroup analyses conducted in patients with LGS and DS treated without CLB, a meta-analysis of pooled data from patients with LGS and DS treated without CLB, the recent TSC results without CLB, and updated real-world evidence from patients, caregivers, and claims data. No new non-clinical or clinical data were generated.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application.

2.3. Clinical aspects

2.3.1. Introduction

In order to support the proposed extension of indication application, no new clinical data were generated and provided.

The data presented to support the extension of indication were subgroup analyses conducted in patients with LGS and DS treated without CLB, an exploratory meta-analysis of pooled data from patients with LGS and DS treated without CLB, the TSC study results and updated real-world evidence.

2.3.2. Pharmacokinetics

The MAH reviewed the existing PK data. No new data were generated.

Similar to the PK data for all patient treated with and without CLB, the PK data in patients treated with CBD-OS without CLB show a high degree of overlap between exposure and metabolite concentration and the PD effect.

The exploratory PK/PD analysis in LGS, and TSC patients demonstrated a flat exposure-efficacy relationship and found a significant degree of overlap in exposure (AUC) between CBD-OS doses administered (25 and 50 mg/kg/day). In the PK/PD assessment in patients with LGS, there was a shallow exposure-efficacy relationship reflecting the lower dose range and near doubling of exposure with a doubling of CBD-OS dose.

The exploratory analysis suggests that there may be a saturation of absorption at doses between 20 to 25 mg/kg/day and above.

Pharmacokinetic interaction studies

in-vitro studies of CBD drug metabolism and physiologically based PK modelling was provided and reviewed in the original MAA. In addition, relevant to this proposed extension of LGS and DS indication, the following DDI studies results were included and reviewed in the original MAA:

- Potential effects of CBD-OS on common ASMs, including CLB, that interact with enzymes involved with CBD metabolism,

- Potential for CYP mediated DDIs using probe substrates to further quantify and refine guidance for prescribers.

In all studies investigating the bidirectional effects of CBD-OS and CLB, there was a consistent increase in plasma concentrations of the active CLB metabolite, N-CLB, of the active CBD-OS metabolite, 7-OH-CBD, and an increase in N-CLB:CLB ratio. The extent of the elevation in N-CLB exposure (Cmax and AUC) with CBD-OS treatment was similar between healthy adult participants, adult epilepsy patients, and pediatric epilepsy patients.

2.3.3. Pharmacodynamics

As reviewed in the original MA, PK analyses in LGS patients using concomitant CLB or not demonstrate an exposure-response relationship for both parent CBD and active metabolite, 7-OH-CBD, in the probability of being a drop-seizure responder. In DS patients, there is no exposure-response relationship demonstrated without CLB.

2.3.4. Discussion on clinical pharmacology

No new data was provided in this application. The MAH claims that the existing PK data is relevant to the proposed extension of indication.

From the existing PK data, it is agreed that increasing CBD-OS doses beyond 25 mg/kg/day did not provide any efficacy advantage but worsened the safety profile in TSC treatment. Similar trend is observed for LGS and DS studies.

There is an inherent interindividual variability in PK of CBD, which supports individualized dose titration to maximize effect for patients.

There is a strong interaction between CBD and N-CLB.

The CHMP agreed that there might be similar exposure-efficacy relationship in LGS patients using concomitant CLB or not. However, it is not possible to demonstrate this relationship for the DS indication. For DS, there is no exposure-efficacy relationship demonstrated without CLB, and PK-PD findings cannot be generalized to different indications.

In addition, positive trend in exposure-efficacy cannot be conclusive in the absence of clinical data supporting a positive B/R for treatment of LGS or DS patients with CBD-OS and without CLB (see also section 2.4.1 - Discussion on clinical efficacy).

2.3.5. Conclusions on clinical pharmacology

The CHMP does not agree that existing PK/PD data are supportive of the proposal to remove the CLB restriction in LGS and DS indications.

2.4. Clinical efficacy

No new clinical efficacy data were generated and provided for this extension of indication application.

Based on the data in patients treated without CLB in the LGS and DS pivotal studies reviewed in the original Marketing Authorisation and in the context of the TSC study GWEP1521 (EMEA/H/C/004675/II/0005), the following analyses were provided:

1 - Independent and clinically relevant effect of CBD-OS without CLB by subgroup and pooled analysis of the patients treated without CLB in the 4 studies in patients with LGS and DS (GWEP1332 CSR Amendment 2017, GWEP1414 CSR Addendum 2018, GWEP1423 CSR Addendum 3 2018, GWEP1424 CSR Amendment 2019) on:

a. Change from baseline in frequency of indication-specific seizures (drop seizures in LGS, convulsive seizures in DS),

b. Frequency of treatment responders (patient showing a ≥ 50% reduction in indication-specific seizures from baseline),

c. Frequency of patients showing ≥ 75% and ≥ 90% reductions in indication-specific seizures from baseline,

d. Change from baseline in frequency of total seizures.

2 - Independent and clinically relevant effect of CBD-OS without CLB in TSC,

3 - Real-world evidence of the clinical benefit of patients using CBD-OS without CLB collected from patients, caregivers, and healthcare claims data.

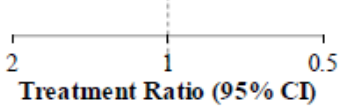
1. Exploratory subgroup analyses performed in the patients treated without CLB in the individual LGS and DS pivotal studies

The LGS and DS pivotal studies were designed to show efficacy in rare, treatment-resistant orphan conditions, where patients are treated with a median of 4 concurrent ASMs. The primary objective was to demonstrate significant reductions in LGS- and DS-associated seizures compared with placebo across all patients. The key secondary endpoint was included to demonstrate that a greater frequency of patients treated with CBD-OS met the 50% responder criteria definition compared to placebo.

Within the LGS studies, all 3 subgroups (treated without CLB by dose [GWEP1423 20 mg/kg/day; GWEP1414 10 and 20 mg/kg/day]) showed directional effects for change on the primary endpoint (drop seizures) in favour of CBD-OS (Figure 4-1).

Figure 4-1 **Reduction in Drop Seizure Frequency During the Treatment Period Compared with Baseline (Treatment Ratio) Among Patients Treated Without Clobazam in Studies GWEP1414 and GWEP1423 (ITT Analysis Set)**

Endpoint Comparison vs. Placebo	Placebo (N)	CBD-OS (N)	Favors Placebo	Favors CBD-OS	Treatment Ratio (95% CI)	P-value
Change in Total Seizure Count						
All LGS Studies						
10 mg/kg/day CBD-OS	39	36			0.710 (0.513, 0.982)	0.0384
20 mg/kg/day CBD-OS	82	84			0.899 (0.727, 1.112)	0.3277
10 + 20 mg/kg/day CBD-OS	121	120			0.837 (0.701, 1.000)	0.0496
GWEP1423						
20 mg/kg/day	43	44			0.924 (0.691, 1.236)	0.5924
GWEP1414						
10 mg/kg/day	39	36			0.710 (0.513, 0.982)	0.0384
20 mg/kg/day	39	40			0.871 (0.636, 1.194)	0.3896



Within the DS studies, all three subgroups (treated without CLB by dose [GWEP1332B 20 mg/kg/day; GWEP1424 10 and 20 mg/kg/day]) showed directional effects for positive change on the primary endpoint (convulsive seizures) in favour of CBD-OS (Figure 4-2).

Figure 4-2 **Reduction in Convulsive Seizure Frequency During the Treatment Period Compared with Baseline (Treatment Ratio) Among Patients Treated Without Clobazam in Studies GWEP1332B and GWEP1424 (ITT Analysis Set)**

Endpoint Comparison vs. Placebo	Placebo (N)	CBD-OS (N)	Favors Placebo / Favors CBD-OS	Treatment Ratio (95% CI)	P-value
Change in Convulsive Seizure Count					
All DS Studies					
10 mg/kg/day CBD-OS	24	21		0.909 (0.593, 1.392)	0.6581
20 mg/kg/day CBD-OS	45	48		0.836 (0.613, 1.141)	0.2589
10 + 20 mg/kg/day CBD-OS	69	69		0.861 (0.670, 1.106)	0.2409
GWEP1332B					
20 mg/kg/day	21	21		0.884 (0.541, 1.444)	0.6197
GWEP1424					
10 mg/kg/day	24	21		0.909 (0.593, 1.392)	0.6581
20 mg/kg/day	24	27		0.805 (0.536, 1.208)	0.2929

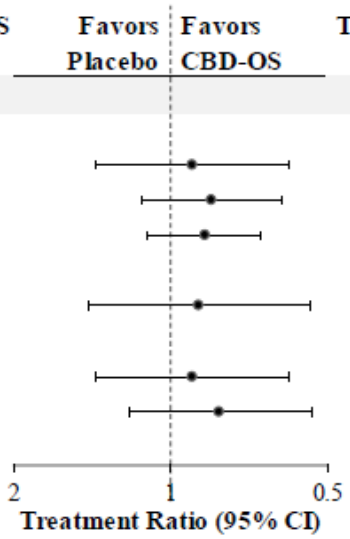


Figure 4-3 and Figure 4-4 present responder estimates, including ORs for both a ≥ 50% and ≥ 75% response level in patients treated without CLB.

Figure 4-3 **Drop Seizure Responders (≥ 25%, ≥ 50%, and ≥ 75% Reductions from Baseline) for Patients Without Clobazam in LGS Trials GWEP1414 and GWEP1423 (ITT Analysis Set)**

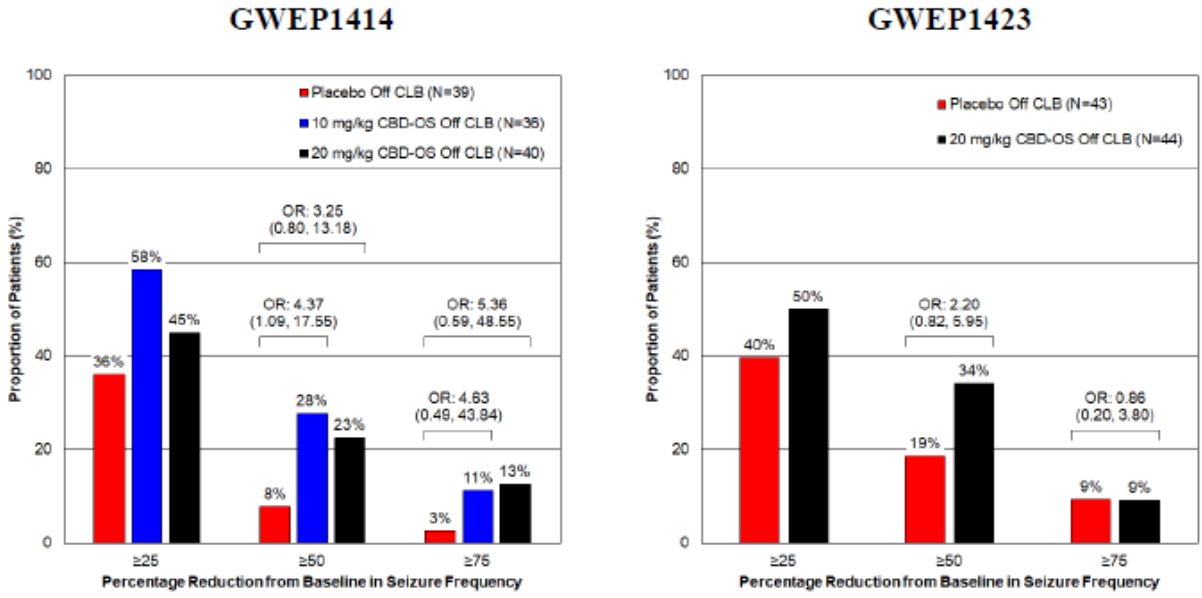
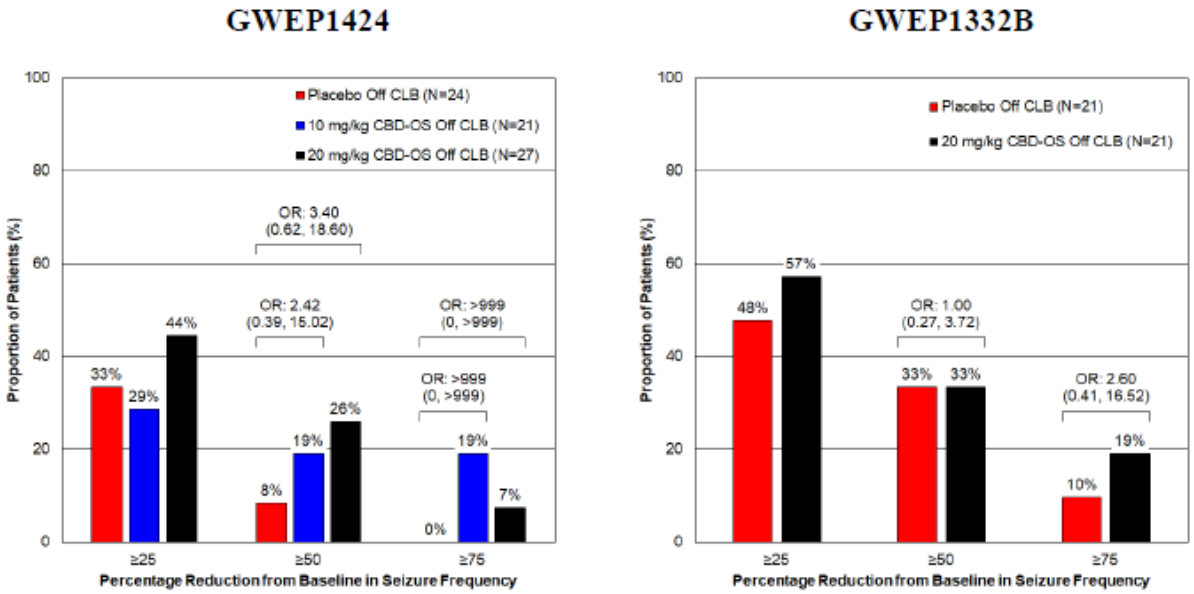


Figure 4-4 **Convulsive Seizure Responders (≥ 25%, ≥ 50%, and ≥ 75% Reductions from Baseline) for Patients Without Clobazam in DS Trials GWEP1424 and GWEP1332B (ITT Analysis Set)**



Analysis performed across trials (pooled analyses and meta-analysis)

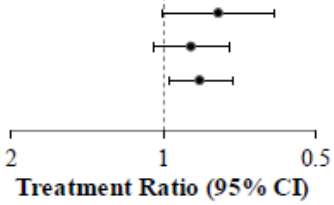
Pooled LGS and DS

The MAH conducted a meta-analysis to investigate whether CBD-OS as an active substance has antiseizure effects when used without CLB. The meta-analysis combined pooled data from the patients treated without CLB from the 4 CBD-OS pivotal studies in patients with LGS or DS and estimated the independent treatment effect of CBD-OS without CLB on primary seizure count (drop seizures in LGS and convulsive seizures in DS), 50% treatment responder rate, 75% treatment responder rate, 90% treatment responder rate, as well as total seizure count.

Estimates of the treatment effect without CLB derived from the pooled-meta-analysis on reduction in primary seizure count are displayed in Figure 4-5.

Figure 4-5 **Reduction in Primary Seizure Frequency During the Treatment Period Compared with Baseline (Treatment Ratio) Among Patients Treated Without Clobazam Across All LGS and DS Studies (ITT Analysis Set)**

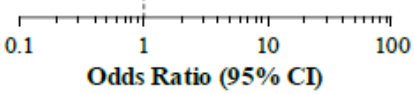
Endpoint Comparison vs. Placebo	Placebo (N)	CBD-OS (N)	Favors Placebo / Favors CBD-OS	Treatment Ratio (95% CI)	P-value
Change in Convulsive Seizure Count					
All LGS + DS Studies					
10 mg/kg/day CBD-OS	63	57		0.777 (0.601, 1.004)	0.054
20 mg/kg/day CBD-OS	127	132		0.879 (0.738, 1.047)	0.1485
10 + 20 mg/kg/day CBD-OS	127	189		0.845 (0.731, 0.977)	0.0226



Estimates of the treatment effect without CLB derived from the pooled-meta-analysis on responder rates are displayed in Figure 4-6.

Figure 4-6 **Forest Plots Estimating the Treatment Difference in Frequency of > 50% Treatment Responders Presented by Dose Among Patients Treated Without Clobazam Across All LGS and DS Studies (ITT Analysis Set)**

Endpoint Comparison vs. Placebo	Placebo (n/N)	CBD-OS (n/N)	Favors Placebo / Favors CBD-OS	Odds Ratio (95% CI)	P-value
≥ 50% Responders					
All LGS + DS Studies					
10 mg/kg/day CBD-OS	5/63	14/57		3.52 (1.16, 10.63)	0.0259
20 mg/kg/day CBD-OS	20/127	38/132		2.11 (1.11, 3.99)	0.0221
10 + 20 mg/kg/day CBD-OS	20/127	52/189		2.40 (1.38, 4.16)	0.0020



TSC

Similar to the results of the LGS and DS studies, TSC patients in study GWEP1521 who were treated with concurrent CLB showed the largest treatment response to CBD-OS. However, most patients in study GWEP1521 were not taking concurrent CLB [n = 163/224 (73%)] and treatment with CBD-OS produced a 30% greater treatment effect on the primary endpoint (TSC-associated seizures) compared to placebo (Treatment Ratio = 0.70, p<0.001).

The TSC-associated primary endpoint included both focal and generalized (tonic–clonic, tonic, clonic, and atonic) seizure types. Exploratory analysis of the effect of CBD-OS on the two seizure types included in the primary endpoint calculation were consistent with the results obtained for the primary endpoint. There was a statistically significant 27% greater reduction in focal seizures in patients treated with CBD-OS without CLB compared with placebo (Treatment Ratio = 0.73, p=0.04) and a statistically significant 36% greater treatment effect in reduction of generalized seizures (Treatment Ratio = 0.64, p=0.03).

Patients in GWEP1521 who were treated with CBD-OS without CLB experienced a nominally significant 25% greater reduction in TSC-associated seizures compared to patients treated with placebo (Treatment Ratio [95% CI] = 0.75 [0.59, 0.96], p=0.02).

3. Other data

Additional data on treatment of CBD-OS without CLB for LGS and DS was collected from 4 sources:

- Overall and subgroup efficacy results of an OLE study (GWEP1415) that enrolled 681 patients who completed the LGS and DS pivotal studies,

- Findings from the US and Australian expanded access programme, which provided CBD-OS treatment to 914 patients with intractable epilepsy, including 127 patients with LGS and 74 patients with DS,

- Results of a retrospective observational study of US claims data assessing healthcare resource utilization associated with CBD-OS use among 419 patients with refractory epilepsy without evidence of CLB use,

- Survey findings from 498 caregivers of patients with LGS or DS treated with CBD-OS with and without CLB.

The aim of OLE study GWEP1415 was to assess the long-term safety of CBD-OS as an adjunctive treatment for either LGS or DS. The study enrolled patients with LGS from studies GWEP1414 and GWEP1423 and patients with DS from study GWEP1332B. Patients were re-titrated at the start of the OLE up to the study's maximum dose of 30 mg/kg/day and maintained on treatment until commercial product was available (analyses were conducted up to 24 months). Rates of CBD-OS discontinuation were 35.3% for patients treated with CLB and 45.7% for patients treated without CLB.

2.4.1. Discussion on clinical efficacy

In this application, the MAH did not provide any new clinical evidence from randomized controlled studies in the LGS and DS indications. All analyses provided are exploratory in nature and consists of data previously evaluated by CHMP in the original MAA.

Main trials in the original MA

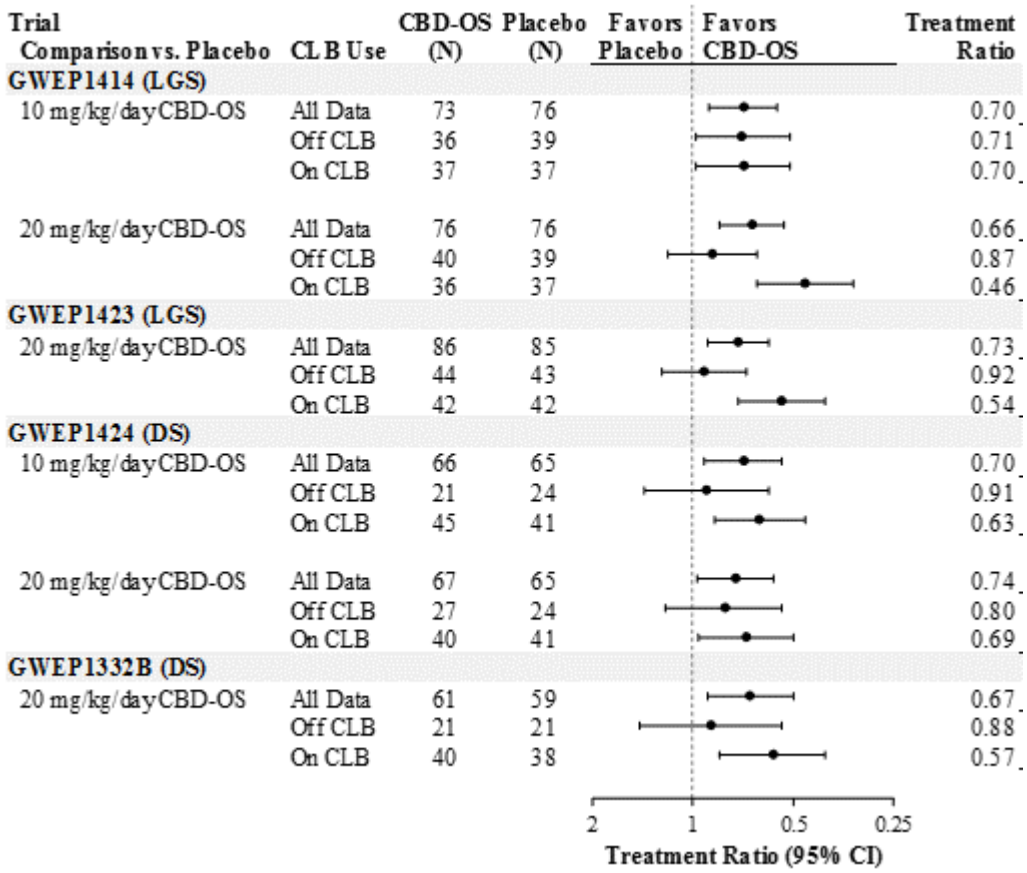
The pivotal trials for LGS and DS in the original MAA were all designed as double-blind parallel-group placebo-controlled trials with a baseline period of 4 weeks and a treatment period of 14 weeks (titration phase 2 weeks, maintenance phase 12 weeks), after which the patients either entered an open-label extension study or (upon completion/withdrawal) tapered the dose over a 10-day period with a safety follow-up 4 weeks after final dose.

In order to be eligible for the LGS trials, patients had to be aged 2–55 years with a clinical diagnosis of LGS. Patients must have had at least 2 drop seizures each week during the first 28 days of the baseline period and have a history of slow (< 3.0 Hz) spike-and-wave pattern in an EEG prior to their enrolment into the baseline period. Patients must have been taking 1 or more AEDs at a dose which had been stable for at least 4 weeks prior to screening and have documented failures on more than 1 AED. The predefined primary endpoint was the percentage change from baseline in drop seizure frequency. There were 3 prospectively defined key secondary endpoints: (1) the proportion of patients who achieved 50% reduction in drop seizures (responder analysis); (2) the percentage change from baseline in total seizure frequency; and (3) the Subject/Caregiver Global Impression of Change (S/CGIC) at last visit. These endpoints were tested hierarchically in the above order following analysis of the primary endpoint.

In order to be eligible for the DS trial, patients had to be aged 2-18 years with a clinical diagnosis of Dravet Syndrome confirmed by a committee of independent experts and had to have experienced 4 or more convulsive seizures during the 4-week baseline period. Patients must have been taking 1 or more AEDs at a dose which had been stable for at least 4 weeks prior to screening. The primary endpoint was the percentage change or change from baseline in convulsive seizure frequency (average per 28 days)

during the treatment period for CBD-OS compared with placebo. A continuous variable rather than a dichotomised variable (responder analysis) was chosen due to the rareness of DS. For the purpose of the EU submission, the 50% responder rate was the key secondary endpoint in Study GWEP1332B which is considered acceptable. For the EU submission only, the secondary endpoints in Study GWEP1332B were tested hierarchically, starting with the key secondary endpoint followed by all other secondary endpoints. In Study GWEP1424, a hierarchical gate-keeping procedure was used to control the type I error starting with the primary endpoint for the 20 mg/kg/day dose followed by the 10 mg/kg/day dose, then the 1st key secondary endpoint for the 20 mg/kg/day dose etc.

The primary endpoint was met in all four studies with an approximately 40-50% median reduction in the active groups as compared to approximately 15-25% in the placebo groups. Specifically for 20 mg/kg dose, as the recommended treatment dose, the clear separation of subgroups according to concomitant CLB use and significant increase in the effect size was noted (see figure below). Whereas it is questionable whether a median difference of 20-25% may in itself be considered clinically relevant, in the LGS studies the primary analysis was supported by key secondary analyses including responder analyses and global impression of change. In terms of drop seizure free days, the treatment difference in LGS corresponded to 3-5 drop seizure free days per 28 days. In DS, the key secondary endpoint (responder analysis) was not met in Study GWEP1332B. In Study GWEP1424, the key secondary endpoint analyses supported the primary analyses.



There is not a clear biological rationale for expecting rather similar effect sizes in these two different indications. Dravet Syndrome is usually associated with SCN1A mutations, and may likely be considered a sodium channel disorder, whereas SCN1A mutations are usually not seen in LGS. It may be that CBD-OS has unspecific anticonvulsive properties, but methodological and pharmacokinetic issues must be considered as well.

At least some of the treatment difference may likely be ascribed to the pharmacokinetic interaction with clobazam (leading to increased clobazam active metabolite N-CLB concentrations). CBD-OS and clobazam have a complex 2-way metabolic interaction. CBD-OS inhibits CYP2C19 which is required to metabolise the active clobazam metabolite N-CLB. This leads to a several fold increase in N-CLB concentration, and since N-CLB has an anticonvulsant effect of 20-100% of its parent compound, clobazam, the resulting anticonvulsant effect might well correspond to a doubling of the clobazam dose, enough to explain a treatment difference of the observed size. In the 3 pivotal trials, there was substantial clobazam concomitant treatment at baseline (approximately 50% in LGS and 65% in DS).

In order to support this proposed extension of indication with the removal the concomitant administration of CLB, the MAH performed various analyses intended to demonstrate independent efficacy of CBD-OS. However, in all pivotal trials, performing the primary analysis on the subgroup of patients with CLB and the subgroup of patients without CLB consistently revealed statistically significant treatment differences in the CLB subgroups but no differences in the non-CLB subgroups. Thus, the isolated efficacy of the CBD-OS and the clinical relevance of such efficacy remained undetermined in LGS and DS patients treated with CBD-OS without CLB. Similarly, the key secondary endpoints showed no support (GWEP1332B) or only directional support.

The clinical relevance of the effect in patients not receiving CLB was subject of discussion in a Scientific Advisory Group at the time of the original MAA. Overall, the SAG experts expressed doubts about the validity of the efficacy data and were not convinced that efficacy of CBD-OS without CLB had been reliably demonstrated in statistical terms. Notwithstanding this, the group consisting of experts in the field, were split in the interpretation of the clinical relevance of the observed effect. Approximately half of the group did not consider the observed effect clinically relevant whereas the other half did indeed consider the effect clinically relevant if data were to be considered reliable. Furthermore, as LGS and DS patients present a multitude of different types of seizures, the clinical relevance of a 50% reduction in one type of seizure frequency was questioned by some experts. The SAG did not support the MAH's claim that the observed smaller effect of CBD-OS in patients off CLB was due to these patients constituting a therapy resistant subgroup.

Supportive data

Pooled LGS-DS meta-analysis

As previously asserted, the CHMP maintains that pooling across different endpoints (LGS-associated seizures, DS-associated seizures) and doses (10 and 20 mg/kg/day) relies on assumptions that the antiseizure response across both doses and conditions are equivalent. The MAH is of the view that there is no evidence of a dose-response relationship between 10 and 20 mg/kg/day and no difference between 10 and 20 mg/kg/day in time to onset of effects (Madan Cohen 2020, Privitera 2021, Wu 2020), and that this does not *per se* suggest that the magnitude of effect at 10 and 20 mg/kg/day is equivalent but would support dose pooling in a meta-analysis. This is not agreed as pooling in a meta-analysis not only across different trials but also across different indications assumes that the treatment is equally effective in different indications, which is not the case as demonstrated across trials in LGS, DS. TSC, Rett syndrome.

In the pooled analysis, the number of patients treated with placebo (n=127) and CBD-OS without CLB (n=132) reach the levels evaluated in pivotal studies in orphan epilepsy indications. Nevertheless, the primary endpoint used in the pivotal studies, which is primary seizure count (drop seizures in LGS and convulsive seizures in DS), still does not demonstrate a statistically or clinically meaningful difference between placebo and active arms with the recommended dose 20 mg/kg/day in the absence of CLB (despite large enough numbers). The meta-analysis estimated that **"**across indications and doses**"** CBD-OS without CLB is associated with a 15% reduction in indication-specific seizures. Regardless of the uncertainties in individual trials and issues with pooling data across indications and doses, the size of effect of CBD-OS without CLB is not considered statistically (nominal) or clinically significant.

In addition, there is an increased safety concerns in patients using recommended dose of CBD-OS without CLB: The greater magnitude of CBD-OS treatment effect without CLB in patients treated with 10 mg/kg/day compared to 20 mg/kg/day in the meta-analysis is partially explained by paradoxical increase in seizures while increasing dose of CBD-OS from 10 to 20 mg/kg/day. It remains unclear, however, why some patients with LGS experienced seizure increases when force titrated to 20 mg/kg/day, as this increase in seizures was unique to the 2 LGS studies treated without CLB (GWEP1414, GWEP1423) and was not replicated in patients treated with CLB in the LS, or in patients treated with or without CLB in the DS or TSC pivotal studies, even at doses as high as 50 mg/kg/day.

TSC data

The TSC data cannot validate the independent effect of CBD-OS without CLB in LGS and DS populations.

Most patients in study GWEP1521 were not taking concurrent CLB [n = 163/224 (73%)] and yet treatment with CBD-OS produced a 30% greater treatment effect on the primary endpoint (TSC-associated seizures) compared to placebo (Treatment Ratio = 0.70, $p<0.001$).

The TSC-associated primary endpoint included both focal and generalized (tonic–clonic, tonic, clonic, and atonic) seizure types. Exploratory analysis of the effect of CBD-OS on the two seizure types included in the primary endpoint calculation were consistent with the results obtained for the primary endpoint. There was a statistically significant 27% greater reduction in focal seizures in patients treated with CBD-OS without CLB compared with placebo (Treatment Ratio = 0.73, $p=0.04$) and a statistically significant 36% greater treatment effect in reduction of generalized seizures (Treatment Ratio = 0.64, $p=0.03$).

Patients in GWEP1521 who were treated with CBD-OS without CLB experienced a nominally significant 25% greater reduction in TSC-associated seizures compared to patients treated with placebo (Treatment Ratio [95% CI] = 0.75 [0.59, 0.96], $p=0.02$).

Hence, in the TSC application (EMEA/H/C/004675/II/0005), CHMP concluded on statistically and clinically relevant effect of CBD-OS in TSC indication.

However, this effect cannot be extrapolated to different indications and, in the absence of conclusive clinically relevant effect observed in clinical studies, it cannot be considered as supportive data for amending the LGS and DS indications.

Other data

The additional data, from non-randomised studies with US LGS and DS patients (expanded access program, US caregiver survey, US claims data) and other considered types of epilepsies (US claims) should be interpreted with caution due to confounder variables and the observational character of data collection. These data cannot be considered supportive in the absence of established positive benefit/risk in the pivotal studies.

During the procedure, a cross-study comparison of fenfluramine and CBD-OS without CLB in LGS was also provided and showed little difference in the result. This cross-study comparison, for two different products, is however methodological limitation and cannot be use as a basis for approval.

2.4.2. Conclusions on the clinical efficacy

No new clinical efficacy data were generated to support the removal of concomitant CLB for the LGS and DS indication.

There is no conclusive statistically and clinically relevant effect observed with CBD-OD treatment without CLB in the individual pivotal trials for LGS and DS, as reviewed during the original MAA.

2.5. Clinical safety

No new clinical safety data were generated and provided for this extension of indication application.

The safety profile for CBD-OS in the approved indications has been established from 4 placebo-controlled studies in patients with LGS and DS, and 1 placebo-controlled study in patients with TSC, and their associated long-term OLE studies. To date, no new important safety concerns have arisen from an estimated 38,200 patient-years of post-marketing experience with CBD-OS according to MAH.

In the placebo-controlled studies in LGS and DS, concomitant CLB treatment was associated with an overall increased safety risk. Table 5-1 shows that there were consistently higher frequencies of AEs, SAEs at both the 10 and 20 mg/kg/day dosages, and AEs leading to discontinuation at the 20 mg/kg/day dosage, among patients treated with CLB compared to patients treated without CLB.

Table 5-1 **Incidence of Treatment-emergent Adverse Events, Serious Treatment-emergent Adverse Events and Treatment-emergent Adverse Events Leading to Discontinuation by Clobazam Use in Controlled DS and LGS Studies (Pool DS/LGS)**

	With-CLB Patients with LGS or DS				Without-CLB Patients with LGS or DS			
Event (%)	Placebo (N=164)	CBD-OS 10 mg/kg/d (N=85)	CBD-OS 20 mg/kg/d (N=167)	All CBD-OS (N=258)	Placebo (N=128)	CBD-OS 10 mg/kg/d (N=54)	CBD-OS 20 mg/kg/d (N=140)	All CBD-OS (N=198)
Any AE	79.9%	88.2%	94.0%	92.2%	71.1%	77.8%	85.7%	82.8%
Any SAE	9.1%	22.4%	22.8%	22.5%	8.6%	16.7%	16.4%	16.2%
Any AELD	0.6%	1.2%	12.6%	8.5%	1.6%	1.9%	8.6%	6.6%

The increased safety risk in patients treated with CBD-OS with CLB compared to treatment without CLB was primarily driven by the increased frequency of important risks relating to somnolence/sedation, pneumonia, and rash. Approximately half of the patients treated with CBD-OS with CLB experienced clinically significant somnolence, fatigue, lethargy, and sedation regardless of whether CBD-OS was administered as 10 or 20 mg/kg/day. CBD-OS treatment with CLB was also associated with higher incidences of pneumonia, rash, aggression, and irritability (Table 5-2).

Table 5-2 Incidence of Key Adverse Events of Special Interest by Clobazam Use in Controlled DS and LGS Studies (Pool DS/LGS)

Combined Preferred Terms	With-CLB Patients with LGS or DS				Without-CLB Patients with LGS or DS			
	Placebo (N=164)	CBD-OS 10 mg/kg/d (N=85)	CBD-OS 20 mg/kg/d (N=167)	All CBD-OS (N=258)	Placebo (N=128)	CBD-OS 10 mg/kg/d (N=54)	CBD-OS 20 mg/kg/d (N=140)	All CBD-OS (N=198)
Somnolence, Fatigue, Lethargy, Sedation AESI	20.7%	47.1%	57.5%	54.3%	12.5%	13.0%	23.6%	20.2%
Rash, Generalized maculo-papular rash AESI	3.7%	10.6%	12.0%	11.2%	1.6%	3.7%	5.0%	5.1%
Pneumonia AESI	1.2%	14.1%	7.2%	9.3%	1.6%	0	2.9%	2.0%
Aggression, Irritability AESI	2.4%	10.6%	10.2%	10.1%	2.3%	5.6%	7.1%	6.6%

In particular, regarding the grouped AESI terms for pneumonia:

Table 3: Frequency of Grouped AESI Terms of Pneumonia with and without Clobazam Use

	DS/LGS, No. of Patients (%)			TSC, No. of Patients (%)			DS/LGS/TSC	
	CBD-OS			CBD-OS				
Number of patients with at least one Grouped Term Pneumonia	10 mg/kg/day (N1 = 85, N2 = 54)	20 mg/kg/day (N1 = 167, N2 = 140)	Placebo (N1=164, N2=128)	25 mg/kg/day (N1 = 18, N2 = 57)	50 mg/kg/day (N1 = 20, N2 = 53)	Placebo (N1=25, N2=51)	All CBD-OS (N1 = 296, N2 = 308)	Placebo (N1 = 189, N2 = 179)
With CLB	14.1%	7.2%	1.2%	16.7%	5.0%	0	9.5%	1.1%
Without CLB	0	2.9%	1.6%	0	1.9%	2.0%	1.6%	1.7%

Abbreviations: AESI = adverse event of special interest; CBD-OS = cannabidiol oral solution; CLB = clobazam; DS = Dravet syndrome; LGS = Lennox–Gastaut syndrome; N1 = participants with CLB; N2 = participants without CLB; TSC = tuberous sclerosis complex.
Source: ISS-Tuberous Sclerosis Pooled DSLGSTSC Tables - Table DSLGSTSC.47.5.20.

2.5.1. Discussion on clinical safety

No new safety information was submitted by the MAH.

The main safety issues with CBD-OS in the recommended dose range of 10 to 25 mg/kg/day are hepatotoxicity and effects on the CNS such as increase in seizures (including paradoxical increase with 20 mg/kg/day dose), somnolence, sedation, lethargy, fatigue, irritability and aggression. Other safety issues include infections, decreased appetite, weight decrease, diarrhoea, pyrexia, vomiting.

The safety profile, including the side effects linked to the CLB treatment, is known and the treating physicians are informed and experienced about handling these issues. In the absence of established efficacy profile, a known and manageable safety profile cannot be decisive on change of indication

In view of the increased risk of pneumonia observed in the pivotal trials, the CHMP agreed to amend the SmPC sections 4.8 in order to better inform the prescribers.

2.5.2. Conclusions on clinical safety

In line with the original MAA, CBD-OS use with CLB has a known safety profile.

In view of the increased risk of pneumonia, the CHMP agreed with the update of the Product Information.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

Following the CHMP position that the proposed extension of indication was not approvable, the RMP version 3.0, with minor editorial updates, was agreed.

2.7. Update of the Product information

As a result of the extension of indication assessment and following the CHMP opinion that the positive B/R risk of CBD-OS without CLB is not statistically and conclusively demonstrated, the Epidyolex indication remains unchanged.

Nevertheless, the CHMP considered appropriate an update of Section 4.8 of the SmPC in order to provide further details regarding the increased risk of pneumonia.

In addition, the outcome of the P46 011.1 procedure, as concluded in January 2023, was reflected in the section 5.1 of the SmPC.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

No new non-clinical, clinical efficacy or safety data were submitted to support the proposed extension of indication, with the use of CBD-OS as adjunctive therapy of seizures associated with LGS or DS without the restriction of concomitant CLB.

The MAH referred to sections of data, previously generated and reviewed by the CHMP in the original MAA, in patients treated without CLB in the LGS and DS pivotal studies. The MAH also referred to the TSC data (study GWEP1521). A cross-study comparison of fenfluramine and CBD-OS without CLB in LGS was also provided during the procedure. The MAH argued that CBD-OS independent efficacy for broad spectrum symptomatic seizure reductions are established in TSC Study GWEP1521, that the safety profile of CBD-OS without CLB is favourable and that there is a need for expert physicians to select the most appropriate course of treatment for their patients.

Whereas the clinical relevance of any seizure reduction in LGS/DS are acknowledged, all analyses provided in this application are exploratory in nature and consist of data previously evaluated by CHMP.

There is no conclusive clinically relevant effect observed with CBD-OD treatment without CLB in the individual pivotal trials for LGS and DS. Neither the primary analysis nor the responder analysis is considered reliable or robust in terms of clinical relevance (which are already statistically not significant). *Post hoc* analyses without predefinition are not considered as an adequate approach to generate robust and reliable results. Furthermore, pooled analyses conducted across studies with different study populations, indications, study design and different doses cannot serve relevant proof of intended effect as well.

The data generated for the TSC indication cannot be extrapolated to the LGS/DS indications (different population with different primary efficacy measures (i.e., focal motor seizures in TSC versus drop seizures in LGS and convulsive seizures in DS).

Uncertainties about the effect size and clinical relevance for CBD-OS treatment without CLB in LGS and DS indications remain unchanged. The safety profile of CBD treatment in conjunction with CLB is known to the treating physician and manageable with precautions or discontinuation in certain cases (including the risk of paradoxical increase in seizures with titration to 20 mg/kg/day dose in LGS patients without CLB treatment).

Consequently, in the absence of any new clinical data, the previous review and opinion of the CHMP, including the Scientific Advisory Group expert consultation, in the context of the original MAA, is maintained.

No new data were provided and there is currently insufficient robust data of CBD-OS without concomitant CLB treatment in LGS and DS indications to support the proposed extension of indication. As reviewed and concluded in the original MAA, the overall B/R of Epidyolex remains positive for the indication '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'.

Therefore, based on the assessment of the data contained in the application, the CHMP is of the view that the proposed extension of indication submitted under category C.1.6 of the variation classification Guideline could not be supported. Instead, the data submitted support changes regarding the adverse event pneumonia (SmPC section 4.8).These changes fall under category C.1.4 of the variation classification Guideline.
In reply to the 3rd Request for Supplementary Information, the MAH updated the product information accordingly.

3.1. Conclusions

Based on the assessment of the data contained in this application, the CHMP agrees that whilst the proposed extension of indication, with the use of CBD-OS as adjunctive therapy of seizures associated

with LGS or DS without the restriction of concomitant CLB, cannot be supported, the data submitted support changes regarding the adverse event pneumonia (SmPC section 4.8).

The overall B/R of Epidyolex remains positive 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.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and III

Update of section 4.8 of the SmPC to provide further details regarding the increased risk of pneumonia. In addition, the outcome of the P46 011.1 procedure, as concluded in January 2023, is reflected in the section 5.1 of SmPC. The MAH took the opportunity to implement editorial changes in the product information and the local representative contacts in the Package Leaflet were updated. Version 3.0 of the RMP has also been agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Epidyolex is not similar to Fintepla within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Epidyolex-H-C-004675-II-0020'

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 26 April 2023.

Appendix

1. CHMP AR on similarity dated 26 April 2023.