
in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

# Cannabidiol with clobazam for treatment of seizures associated with Dravet syndrome - Addendum


**Produced by** Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

**Authors**
Marie Westwood, Reviews Manager, Kleijnen Systematic Reviews Ltd, U
Bram Ramaekers, Health Economist, Maastricht UMC
Willem Witlox, Health Economist, Maastricht UMC
Ben Wijnen, Health Economist, Maastricht UMC
Debra Fayter, Systematic Reviewer, KSR Ltd
Steve Ryder, Health Economist, KSR Ltd
Nigel Armstrong, Health Economist, KSR Ltd
Titas Buksnys, Health Economist, KSR Ltd
Gill Worthy, Statistician, KSR Ltd
Kate Misso, Information Specialist, KSR Ltd
Manuela Joore, Health Economist, Maastricht UMC
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

**Correspondence to**
Marie Westwood, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD



**Date completed** 24/09/2019

Following the EMA licence of cannabidiol, the company provided evidence from a subgroup of the trial population (patients treated also with clobazam). The company provided an additional submission following the first appraisal committee (AC) meeting. An updated model was submitted that incorporated several changes in response to the ACD. See below for the ERG comments on this submission.

**Clinical evidence**

Baseline data for the new subgroup (with clobazam) seem unbalanced, with respect to seizure frequency and convulsive seizure frequency, between the CBD 10mg/kg/day and placebo arms. The ERG consider that it is unclear what, if any, effect this may have on the treatment effect.

**Validity of the economic model**

The ERG was able to verify that the company's model produced a null QALY gain under the conditions set out by the company (removing discontinuation of CBD) and agrees that the company was able to demonstrate the symmetry of the model in both arms. It is furthermore reassuring that the company, together with a third party, undertook a significant number of internal validity tests that the model passed. However, there are some remaining concerns about the face validity of model assumptions surrounding the health states that patients return to upon treatment discontinuation. On discontinuation from CBD, it is assumed that patients would transit to the seizure frequency distribution as assumed for placebo (i.e. cycle 2 of the comparator arm). This assumption is viewed as particularly problematic because patients discontinue from all health states, but with higher probabilities in the severe health states, and hence patients' health states might improve upon CBD discontinuation. ERG did provide a scenario analysis in an attempt to explore the impact of this structural assumption (see Table 3). Implementing alternative scenarios is particularly challenging and time consuming due the opaqueness of the economic model. Transparency issues include many hidden worksheets, hidden cells, and coding most of the model in VBA which may not have been necessary and which had changed substantially in producing the latest version of the model. This hampered the ERG's ability to thoroughly validate the model, and explore some assumptions within the model.

**Updates to the company's base case following the ACD**

See below and overview of the company's adjustments along with ERG comments.

**Table 1. Updates to the company's base case following the ACD (source company submission)**

| # | Company update | ACD Response | ERG comment |
|---|---|---|---|
| 1 | The relative treatment effect applied to lifetime in the usual-care arm and for discontinued CBD patients | 3.10, 3.14 | Consistent with ERG preferences (see also ERG report section 5.2.2) |
| 2 | Stopping rules applied at 12 and 24 months, in addition to 6 months, based on NHS England Guidelines (derived from the GWPCARE5 dataset) | 3.7 | This is inconsistent with the committee preferences which preferred applying the stopping rule at 3 months. Moreover, the evidence used to derive the input parameters for the stopping rules is unclear to the ERG. Additionally, it is unclear whether the 2nd and |

| | | | |
|---|---|---|---|
| | | | 3rd stopping points are also included in the company's scenario using a 3 months (instead of 6 months) stopping rule. |
| 3 | Probability allocations and transition probabilities for clinical parameters at baseline and in cycle 1 derived only from the subpopulation of patients on clobazam in the 10 mg/kg/day and placebo arms of GWPCARE2.<br>Transition probabilities for cycles 2-9 in the CBD arm derived only from GWPCARE5. | 3.13 | This update is consistent with the subpopulation of patients on clobazam. |
| 4 | Discontinuation rates in cycles 2-9 for the two most severe health states estimated from withdrawers using pooled estimates from the patient level data in the GWPCARE5 study. | N/A | It is unclear to the ERG why this was adjusted. |
| 5 | Disutility applied for 1 cycle for adverse events of special interest rated as severe on CBD | 3.6<br>3.18 | Incorporating disutilities related to adverse events is in line with ERG preferences. However, the value used (i.e. [redacted] for all adverse events) might be questionable. |
| 6 | Risk ratio for death in the convulsive seizure free health state set to 0.71 | 3.16 | The mortality risk is halved. The ERG critiqued the appropriateness of this risk ratio (ERG report section 5.2.6). In short, the initially reported risk ratio of 0.42 reflects the risk ratio for being seizure-free: presumably this is not restricted to convulsive-seizures only. Hence, it is unclear to what degree this evidence supports the association between number of convulsive seizures and increased epilepsy-related mortality. Halving this risk ratio does not resolve this issue. |
| 7 | Caregiver disutilities calculated from the EQ-5D VAS norms for the UK population for each health state (using utility outcomes from the vignette study) | 3.20<br>3.21 | It is unclear to the ERG how the updated caregiver disutilities are calculated by the company. |
| 8 | An average of 2 caregivers per patient | 3.21 | As mentioned before, if multiple carers are involved, the ERG is not convinced that utility decrements are on an additive scale (e.g., if you would consider the whole family, not everyone will have the same disutility). According to the recent DSU report on caregiver QALYs, there is uncertainty on how caregiver (dis)utilities are best incorporated, and the ERG wishes to highlight that this addition is therefore subject to some uncertainty. |

| | | | |
|---|---|---|---|
| 9 | Disutilities applied to each health state for non-convulsive seizures, estimated from de Kinderen 2016 | 3.8 | The main ERG concerns relate to input parameters used for the convulsive-seizure free health state that may reflect that patients are also non convulsive-seizure free (which was not the case). Particularly input parameters related to mortality (both SUDEP and non-SUDEP) and utility values (see also ERG report section 5.2). Therefore, separately capturing non-convulsive seizures likely results in double counting.<br>Moreover, the ERG could not reproduce the utility values retrieved from Kinderen et al (the disutility values retrieved by the ERG were smaller). Furthermore, there may be another issue with double counting as the study of De Kinderen et al. assumed seizure reduction from all seizures (not restricted to non-convulsive seizures). |

**Additional ERG comments**

Dosing of CBD is calculated based on patients' weight. The company used the median instead of mean weight to inform this calculation, arguing that the weight distribution was skewed. However, in clinical practice, outlier patients will also be encountered and therefore the ERG, in line with the committee, considers the mean weight more relevant than the median weight (as explored by the company in a scenario).

As mentioned before, the plausibility of the company's the assumptions for longer-term discontinuation (from cycle 10 onwards), adjusting these parameters to 5% per cycle in all 'seizure' health states, is unclear to the ERG. The ERG would prefer to use identical longer-term discontinuation probabilities as was used for cycles 2-9 (i.e. based on the GWPCARE5 trial).

The company performed a 'waning effect' scenario. This scenario assumes that patients after long-term discontinuation (from cycle 10) incur an additional cycle (3 months) of CBD treatment cost. The ERG would have preferred the treatment waning scenarios as implemented by the ERG (see ERG report).

**Additional ERG analyses**

Due to the lack of time and model transparency, the ERG was only able to perform a specific explorative analyses related to particular issues discussed during the NICE pre-meeting briefing.

**Table 2. Company base-case after ACD (source company submission)**

| Technologies | Total costs (£) | Total QALYs* | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| CCM | £359,041 | -0.0389 | - | - | - |
| CCM + CBD | £393,521 | 1.1391 | £34,479 | 1.1781 | £29,268 |

**Table 3. Company base-case after ACD + ERG scenario exploring the impact of assuming patients would transit to the seizure frequency distribution as assumed for placebo after CBD discontinuation***

| Technologies | Total costs (£) | Total QALYs* | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| CCM | £359,041 | -0.04 | - | - | - |
| CCM + CBD | £402,254 | 0.96 | £43,212 | 1.00 | £43,126 |

* In this scenario the discontinuation rate for CBD is set equal across all health states (mentioned by the company to fix the abovementioned issue) and then calibrated so that the time on CBD is equal to that in the company base-case (with discontinuation rate varying with severity). The calibrated CBD discontinuation rate is 2.19%

## Conclusion

Although the company did implement changes in accordance with the ACD, there remains uncertainty related to the estimated cost effectiveness (as highlighted above).