Cost-effectiveness of Cannabidiol (CBD) for the Treatment of Seizures in Patients With Treatment-Resistant Lennox-Gastaut Syndrome or Dravet Syndrome in the Netherlands

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Introduction

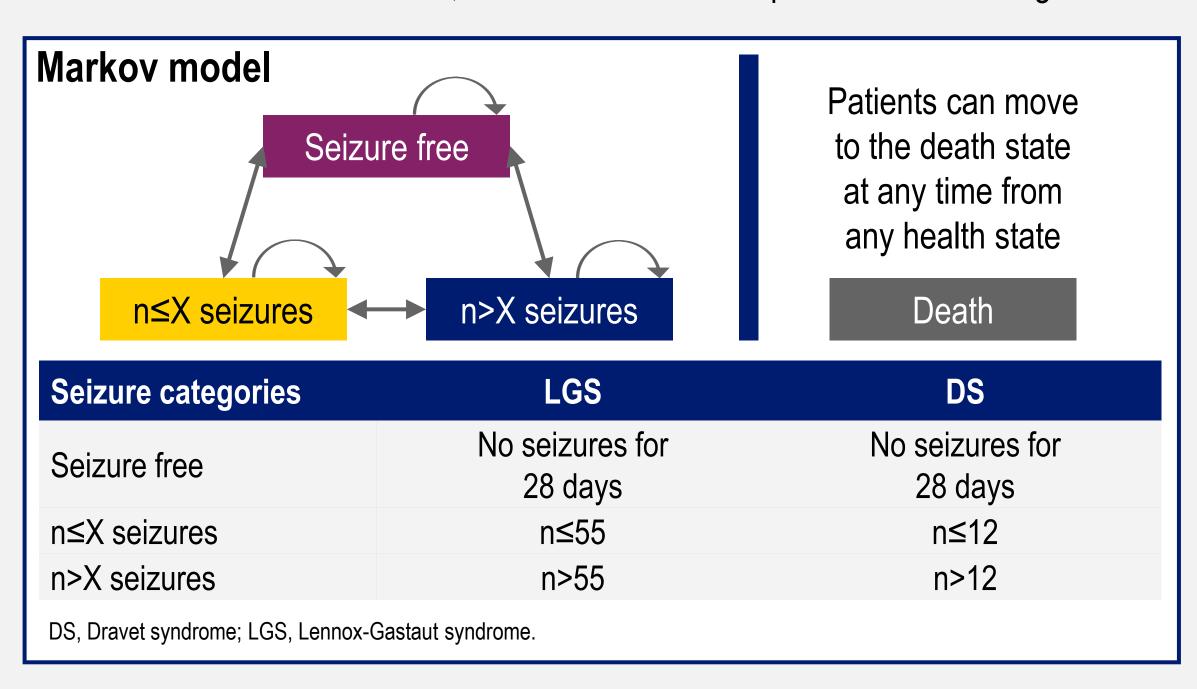
- Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) are rare, lifelong, treatment-resistant, and life-threatening epileptic encephalopathies that present in infancy or early childhood. 1–3
- Complete seizure freedom with antiseizure medications (ASMs) is unachievable in most patients, and there remains a significant unmet need for treatments that reduce seizure frequency and severity and improve the overall condition of patients.^{4,5}
- Plant-derived highly purified cannabidiol (CBD) medicine (Epidyolex®) is approved in the UK and EU for the adjunctive treatment of seizures associated with LGS or DS, in conjunction with clobazam, in patients ≥2 years of age.^{6,7}

Objective

 This study estimated the cost-effectiveness of CBD plus usual care (established clinical management) compared with usual care alone for the treatment of seizures in patients with treatment-resistant LGS or DS in the Netherlands.

Methods

- A cohort-based Markov model was developed to determine the average costs and quality-adjusted life years (QALYs) per patient associated with seizure frequency and seizure-free days.
 - Model analysis was performed over a lifetime (90-year) horizon with a 3-month cycle length from a Dutch societal perspective
- Patients entering the model were treated with either highly purified CBD medicine (Epidyolex®; 100 mg/mL oral solution) at 12 mg/kg/day plus usual care, or usual care alone.
 - Usual care consisted of a variety of ASMs including clobazam
- Baseline characteristics for patients entering the model were based on data across all treatment arms of the randomised controlled trials (RCTs) of CBD for each indication.8-11
- Model health state transition probabilities were based on patient-level data on seizure frequency and seizure-free days from the RCTs and open-label extension (OLE) associated with CBD.8–13
 - Discontinuation and stopping rates associated with CBD treatment were calculated from the RCTs, OLE and/or the US Expanded Access Programme^{8–15}



- Drug acquisition, disease management, adverse events, and societal costs were included, with unit costs sourced from published literature.
- A 2019/2020 price year was used, with costs presented in euros (€); discount rates of 4.0% and 1.5% per annum were applied to costs and outcomes, respectively. 16
- Societal parameters comprised out-of-pocket expenses for both patients and caregivers and included travel costs associated with hospital visits and the time cost of family and professional care.
- Productivity losses were not considered in the analysis since Dutch clinical experts confirmed that most patients with LGS or DS do not work.
- Healthcare resource utilisation data were collected using a UK-based Delphi panel, with estimates validated by Dutch clinical experts.
- Health-related quality of life estimates were collected in Sweden and the UK using vignettes of the general population via time trade-off (TTO) methods¹⁷ and were validated by Dutch clinical experts.
- Parameter uncertainty was assessed via one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA); scenario analyses were conducted to test uncertainty around structural and parametric assumptions.
- This study was conducted with Epidyolex[®], and results do not apply to other CBD-containing products.

Results

- In patients with LGS, CBD plus usual care led to additional costs of €28338 and increased QALYs of 1.318 compared with usual care alone. The resulting incremental cost-effectiveness ratio (ICER) was €21493/QALY.
- In patients with DS, based on the ICER, CBD plus usual care dominated usual care alone, with cost savings of €23642 and increased QALYs of 0.868.
- ICERs for CBD in LGS and DS were in line with the willingness-to-pay (WTP) threshold of €80000/QALY in the Netherlands for these conditions. 18

Base-case and key scenario analyses for LGS and DS

	ICER (€/QALY) of CBD plus usual care vs usual care alone			
Scenario	LGS	DS		
Base case	21493	Dominatinga		
Alternative seizure thresholds ^{b,c}	32051	Dominating ^a		
Time horizon: 20 years	28538	Dominating ^a		
Time horizon: 30 years	24969	Dominating ^a		
Number of caregivers: 2	8272	Dominating ^a		
Mortality RR in seizure-free health state: 0.71	25028	Dominatinga		
Varying the proportion for ICU admissions within hospitalisations: 50% in general ward vs 50% in ICU	20150	Dominating ^a		
Varying the AE disutilities: tripling	21506	Dominating ^a		
Varying the AE costs: tripling	21592	Dominating ^a		
Number of cycles for which AE disutilities are applied: 9 cycles	21523	Dominating ^a		
Utility source: DS utilities (TTO values)	23867	N/A		
Utility source: LGS utilities (TTO values)	N/A	Dominating ^a		
Apply same hours of care for seizure health states	29465	Dominating ^a		

^aCBD plus usual care was clinically superior and cost saving compared with usual care alone. ^bAlternative seizure thresholds for LGS include the following health states: seizure free, ≤84 seizures and >84 seizures (days with seizures). cAlternative seizure thresholds for DS include the following health states: seizure free, ≤25 seizures and >25 seizures (days with seizures). €, euros; AE, adverse event; CBD, cannabidiol; DS, Dravet syndrome; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LGS, Lennox-Gastaut syndrome; N/A, not applicable; QALY, qualityadjusted life year; RR, risk ratio; TTO, time trade-off.

OWSAs for LGS and DS

- Within the OWSAs, the ICER was most sensitive to the average dose of CBD for both LGS and DS.
- The ICER ranged from €9226 to €70561 for LGS, and dominating to €37584 for DS, with all values below the WTP threshold for each indication

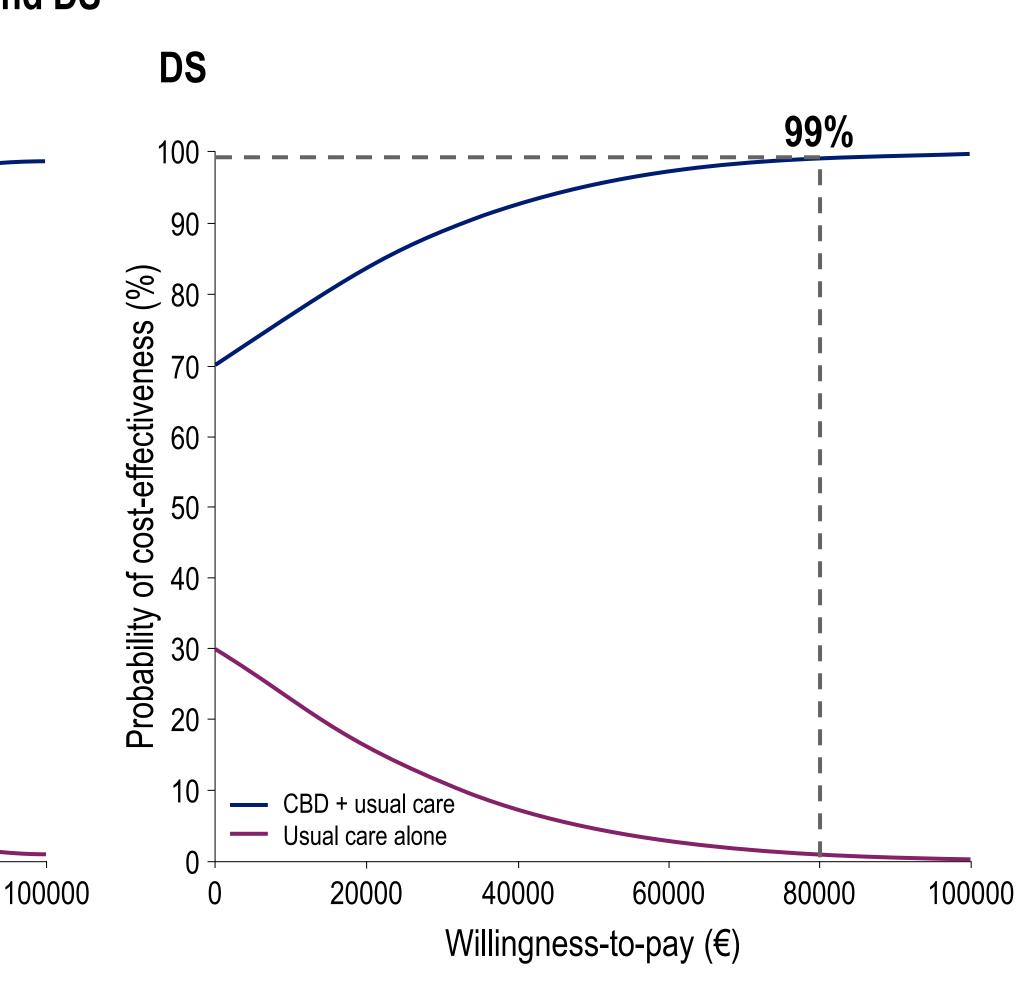
PSAs for LGS and DS

LGS	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)	DS	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Usual care	2,327,078	5.439	-	-	-	Usual care	2,246,536	14.974	_	-	_
CBD	2,357,328	6.772	30251	1.333	22689	CBD	2,223,193	15.850	-23343	0.876	Dominating

€, euros; CBD, cannabidiol; DS, Dravet syndrome; ICER, incremental cost-effectiveness ratio; LGS, Lennox-Gastaut syndrome; QALY, quality-adjusted life year.

Cost-effectiveness acceptability curves for LGS and DS LGS 96% 100 **%** 80 of cost-effectiveness Probability — CBD + usual care Usual care alone

40000



Conclusions

20000

€, euros; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

- The analysis demonstrates that treatment with CBD plus usual care is a cost-effective treatment option in patients with LGS or DS when compared to usual care alone in the Netherlands.
 - Results were robust to sensitivity (OWSA and PSA) and key scenario analyses

60000

Willingness-to-pay (€)

80000

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online. This code is not for promotional adjunctive treatment of seizures associated with tuberous sclerosis complex in patients ≥2 years of age.