Common Drug Review
Pharmacoeconomic Review Report

April 2015

Drug	stiripentol (Diacomit) (capsules and powder for suspension, 250 mg and 500 mg)
Indication	Use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate alone.
Listing request	As per indication
Manufacturer	Biocodex Laboratories

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AED	antiepileptic drug
AWMSG	All Wales Medicines Strategy Group
C$	Canadian dollars
CDR	Common Drug Review
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CLB	clobazam
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
INESSS	Institut national d'excellence en santé et en services sociaux
IQR	interquartile range
NAC	not adequately controlled
NICE	National Institute for Health and Care Excellence
NSF	not seizure free
OCCI	Ontario Case Costing Initiative
OHIP	Ontario Health Insurance Plan
PE	pharmacoeconomic
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
SE	status epilepticus
SF	Seizure free
SMC	Scottish Medicines Consortium
SMEI	severe myoclonic epilepsy in infancy
STP	stiripentol
VPA	valproate

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Stiripentol (Diacomit)
Study Question	To assess, from a Canadian perspective, the economic impact of stiripentol in the treatment of severe myoclonic epilepsy in infancy (SMEI)
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with severe myoclonic epilepsy in infancy (Dravet syndrome) whose seizures are not adequately controlled with the combination of clobazam and valproate
Treatment	Stiripentol 50 mg/kg/day orally in 2 or 3 divided doses daily in conjunction with clobazam (0.5 mg/kg/day) and valproate (25.2 mg/kg/day)
Outcome(s)	Quality-adjusted life-years (QALYs)
Comparators	Combination of clobazam (0.6 mg/kg/day) and valproate (24.5 mg/kg/day)
Perspective	Ministry of health perspective; societal perspective also considered
Time Horizon	5 years
Manufacturer's Results (Base Case)	$50,122 per QALY gained

Key Limitations and CDR Estimate(s)	• CDR noted a number of limitations with the structure and parameters used in the manufacturer's model:
	  ○ CDR was unable to perform reanalyses to assess the impact of structural uncertainty (time horizon, cycle length)
	  ○ Assumption for treatment response in comparator group did not align with efficacy results from STICLO-France and STICLO-Italy clinical trials
	  ○ Assumption that the efficacy of stiripentol after 2 months is maintained over a five-year period and lack of consideration of potential waning of treatment effect
	  ○ Model health state utility values may not be representative of patient population as described in stiripentol clinical trials
	  ○ Inability to adjust for incremental patient weight gains that are inherent to the patient's growth over the model's time horizon
	  ○ Assumption that stiripentol is discontinued after 2 months in patients showing no reduction of seizures might be sooner than what would be expected in clinical practice (3 to 6 months)
	• CDR performed a number of reanalyses to assess the impact of the uncertainty surrounding some of the parameters:
	  ○ Utilities associated with model health states, specifically in health state where seizures are not adequately controlled
	  ○ Stiripentol discontinuation after 2 months in patients showing no reduction of seizures
	  ○ Patient weight gain and resulting impact on costs
	• CDR reanalyses estimate the ICUR for stiripentol, when added to valproate and clobazam, is between $51,160 to $120,419 per QALY, with the best estimate being $104,491 per QALY based on the most likely scenario analysis by CDR

CDR = Common Drug Review; ICUR = incremental cost-utility ratio.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Stiripentol is indicated as an adjunct to clobazam and valproate in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate alone.[1] Stiripentol is available in oral capsules (250 mg and 500 mg) and powder for oral suspension (250 mg and 500 mg sachets). Daily dosage is up-titrated over three days to a recommended dose of 50 mg/kg/day, administered in two to three divided doses. The manufacturer submitted a price of $6.37 per 250 mg capsule or sachet, and $12.73 per 500 mg capsule or sachet, or $38.20 daily, based on a body weight of 30 kg.

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis based on a Markov transitional model over a five-year time horizon. The target population was based on the characteristics of patients in the STICLO trials and the Health Canada indication. The model comprises four health states: not adequately controlled (NAC), not seizure free (NSF), seizure free (SF), and death. NAC is defined as < 50% reduction in seizure frequency from baseline, whereas NSF is defined as ≥ 50% to < 100% reduction in seizure frequency. Patients could stay in the NAC state, move to the NSF or SF state, or die. Transition probabilities between the model health states (NAC, NSF, and SF) were taken directly from the STICLO trials.[2,3] Transition probabilities from NAC, NSF, and SF to death were derived from the results of the DIAVEY study, a stiripentol post-marketing non-interventional study.[4] Cost elements included in the study were: medication costs, change of therapy costs, cost associated with seizure status, and costs used to manage status epilepticus (SE). Utility values were obtained from a study reporting utility values for Lennox-Gastaut syndrome, a form of epileptic encephalopathy that the manufacturer states is comparable to SMEI.

Results of Manufacturer's Analysis

The manufacturer reports that the incremental cost per QALY for stiripentol plus clobazam and valproate therapy was $50,122 compared with clobazam and valproate alone.

Interpretations and Key Limitations

CDR identified the following key limitations with the manufacturer's economic submission:

Assumptions on Patient Response in Comparator Group

The manufacturer assumed that all patients in the comparator group (valproate plus clobazam alone) were in the NAC state (a 50% reduction in seizure frequency) and could transition only to the death state. However, evidence from the STICLO trials shows that between 5% and 9.1% of patients in the valproate plus clobazam–alone group achieved a reduction of at least 50% in the number of seizure episodes.[2,3] A scenario analysis conducted by CDR to examine the impact of varying the distribution of valproate plus clobazam–only patients between the NAC and NSF health states resulted in an increased incremental cost-utility ratio (ICUR) for stiripentol compared with valproate plus clobazam that ranged from $50,861 to $82,645 per QALY.

Health States Utility Values

No published literature is available for utility values in patients with Dravet syndrome. Utility values were based on a conference abstract from a study for Lennox-Gastaut syndrome (Verdian et al.[5]). The Verdian study assessed the number of tonic-atonic seizures, whereas the STICLO study assessed the number of generalized tonic-clonic seizures.[5] The number of seizures at baseline in the utility study was higher than the number of seizures reported at baseline in the STICLO trials.[3] Consequently, utilities used in the economic analysis may be lower than what would be expected for patients having the same characteristics and seizure frequency as those in the STICLO trials. CDR analyses were performed using alternate utility values from the Verdian study[5] as well as from the National Institute for Health and Care Excellence (NICE) guidelines[6,7] that looked into the cost-effectiveness of antiepileptic drug (AEDs) used as monotherapy and adjunctive therapy in the treatment of children with focal epilepsy, leading to ICURs of $58,614 to $120,419 per QALY.

Modelling Patient Weight

The model does not adjust for the expected weight increases that are inherent with patient growth over the five-year time horizon. Increases in patient weight result in increases in stiripentol costs; therefore, the costs of stiripentol in this analysis may be underestimated. Using a patient weight of 45 kg, the ICUR increased to $76,841 per QALY gained.

Long-term Efficacy

The model assumes that the efficacy of stiripentol after two months is maintained over five years and does not consider potential waning of treatment effect. The model did not allow reanalysis to assess the impact of this limitation.

Duration of Treatment

The manufacturer assumed that patients on stiripentol who were NAC after two months of treatments would return to receiving valproate plus clobazam alone;[2] however, according to clinical expert opinion, SMEI patients are expected to receive stiripentol for three to six months before clinical assessments are made to determine stiripentol efficacy. CDR analysis calculated the cost of treatments for the first year to include four months of stiripentol treatment (instead of two), leading to an ICUR of $51,160 per QALY gained.

Results of CDR Analysis

CDR reanalyses on the assumptions outlined previously produced ICURs ranging from $51,160 to $120,419 per QALY gained, with the model being sensitive to variations in utility values associated with the model's NAC health state, as well as to the percentages of patients responding to valproate plus clobazam therapy alone, and patient weight. In a CDR analysis on the most likely scenario based on the limitations and assumptions explained earlier, and in consultation with the clinical expert, the ICUR for stiripentol when added to valproate plus clobazam increased to $104,491 per QALY gained.

Conclusions

A number of limitations with the manufacturer's economic submission were identified. When accounting for them, CDR found that the ICUR for stiripentol compared with valproate plus clobazam ranged from $51,160 to $120,419 per QALY gained, with a most likely ICUR estimate of $104,491 per QALY gained.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

"…The objective of this study was to assess, from a Canadian perspective, the economic impact of stiripentol in the treatment of SMEI."

(Manufacturer's pharmacoeconomic submission, page 12.[8])

1.2 Treatment

Stiripentol, as an adjunct to valproate plus clobazam, at the recommended dose of 50 mg/kg daily, administered in two to three divided doses.

1.3 Comparators

The economic evaluation submitted by the manufacturer compared stiripentol in combination with valproate plus clobazam to a treatment group of valproate plus clobazam alone.

1.4 Type of Economic Evaluation

The manufacturer's cost-utility analysis as per CADTH's *Guidelines for Economic Evaluations of Health Technologies*. The analysis takes a ministry of health perspective. The manufacturer also submitted a cost-utility analysis from a societal perspective.

1.5 Population

The target population for this economic evaluation comprises patients with SMEI whose seizures are not adequately controlled (NAC) with clobazam plus valproate alone. This is in line with the Health Canada indication. The target population presented the mean characteristics of patients included in the randomized STICLO trials, specifically, average patient weight of ± 30kg and median of 4.5 seizures per week at baseline.[2,3,8]

2. METHODS

A cost-utility analysis was conducted using a Markov transition model to assess the cost-effectiveness of stiripentol plus valproate plus clobazam compared with valproate plus clobazam in the treatment of SMEI. The Markov model simulates the course of patients whose seizures are NAC with valproate plus clobazam alone, receiving an adjunctive therapy with stiripentol. The health state transition model comprises four health states: not adequately controlled (NAC), not seizure free (NSF), seizure free (SF) and death. NAC is defined as < 50% reduction in seizure frequency from baseline, whereas NSF is defined as ≥ 50% to < 100% reduction in seizure frequency. The length of each Markov cycle was 1 year for the whole study period. Specifically, patients could stay in the NAC state, move to the NSF or SF state, or die.

The transition probabilities from NAC to NSF or SF states were taken directly from STICLO trials[2,3] as stated by the manufacturer. For transition probabilities for patients who stay in the NAC state or move to the NSF or SF states, they were sourced from clinical trials, minus the patients who died annually. For the transition probabilities from NAC, NSF, and SF to death, the manufacturer stated they were derived

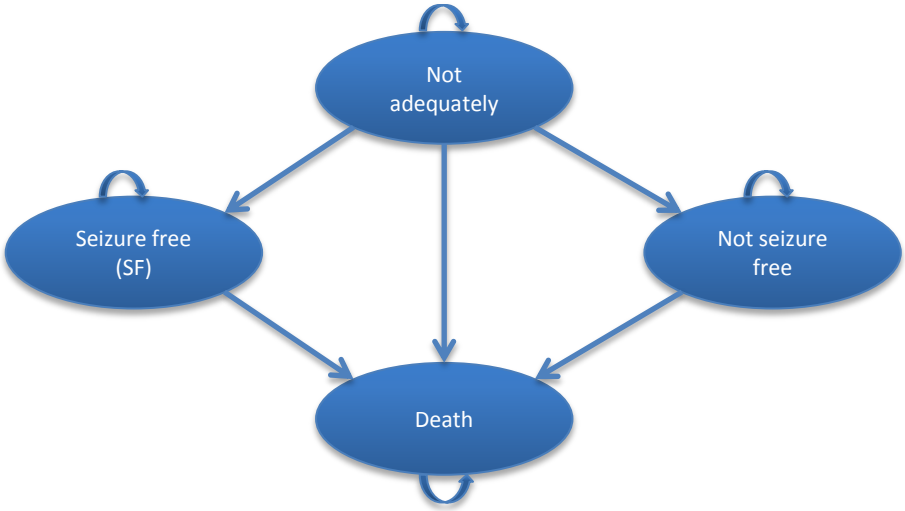
from the results of the stiripentol post-marketing study, DIAVEY.[4] In the DIAVEY study, patients newly prescribed stiripentol were recruited between 2007 and 2012 in 11 European countries. Only French data were used by the manufacturer, as France used stiripentol as adjunctive therapy to valproate + clobazam at 50 mg/kg/day during the DIAVEY study, which corresponded to the Canadian indication. In the French cohort, 61 SMEI patients were exposed to stiripentol for a mean duration of 28 months, during which three patients died. This mortality rate corresponds to an annual mortality rate of 2.1% for SMEI patients treated with stiripentol. In addition, it is known that patients with seizures have a higher mortality risk than patients without seizures. NICE guidelines for economic evaluations of AEDs used a hazard ratio of 0.7 for epileptic patients without seizures, compared with epileptic patients with seizures. The same ratio was used in the present evaluation, leading to an annual mortality rate of 2.4% for patients with seizures and 1.7% for patients without seizures (see equation below). As in NICE epilepsy guidelines, it was assumed that patients NAC (less than 50% reduction in seizure frequency) and patients who were not seizure free (NSF) (50 to 99% reduction in seizure frequency) had the same annual mortality rate.

The manufacturer's model assumes that after two months, patients stay in the same health state (NAC, NSF, SF), except to reach the state of death. This was based on the STICLO trials that indicated stiripentol treatment lasted two months.[2,3] After two months, the model assumes patients who are NAC with stiripentol plus valproate and clobazam would return to valproate and clobazam only. The manufacturer stated that mortality risk varied according to health states (NAC, NSF, SF), but not according to treatments. Also, the manufacturer's model did not include adverse events (AEs), as they were considered by the manufacturer to be negligible and easily manageable through valproate and mainly clobazam dose reduction.

2.1 Model Structure

The manufacturer submitted a Markov transition model which simulates the course of patients whose seizures are NAC with valproate plus clobazam alone, receiving an adjunctive therapy with stiripentol (Figure 1). Transition probabilities from NAC to NSF and NSF were derived from the SITCLO studies,[2,3] while transition probabilities from the NAC, NSF, or SF to death were derived from the results of the DIAVEY post-marketing study.[4]

FIGURE 1: STIRIPENTOL COST-EFFECTIVENESS MODEL STRUCTURE



Source: Manufacturer's Pharmacoeconomic Evaluation Report.[8]

2.2 Clinical Inputs

The manufacturer stated that clinical inputs were derived from the two STICLO trials.[2,3] In the STICLO trials, SMEI patients were treated double-blind for two months with either stiripentol or placebo added to a combination treatment of valproate and clobazam. Combining STICLO-France and STICLO-Italy data, 33 patients were randomized on stiripentol at a fixed dose of 50 mg/kg/day, and 31 patients were randomized on placebo as adjunctive therapy to valproate plus clobazam. After two months on stiripentol plus valproate plus clobazam, 10 (30.3%) patients were NAC, 11 (33.3%) were NSF (50% to 99% reduction on seizure frequency), and 12 (36.4%) were seizure free (SF). In the comparative group, two patients responded to the placebo.

2.2.1 Costs

The costs included in the analysis were: medications; health care resources associated with a change of therapy; health care resources associated with seizure status; and health care resources used to manage status epilepticus (SE).

2.2.2 Medication Costs: Stiripentol, Valproate, and Clobazam

The use of stiripentol, valproate, and clobazam was based on data from the STICLO trials. Treatment costs were assumed to be the same for each cycle of the model, except when patients change therapy, since the model assumes that patients on stiripentol plus valproate plus clobazam who were not adequately controlled after two months of treatment would return to valproate plus clobazam only; therefore, the treatment cost for the first year encompassed costs of two months of stiripentol plus valproate plus clobazam therapy, and costs of 10 months of valproate plus clobazam therapy for patients in the NAC state. For the four subsequent years, treatment cost for patients in the NAC state was the one of valproate plus clobazam alone. The cost of stiripentol was provided by the manufacturer at $0.0255 per mg. The unit cost of the other treatments was the wholesale price in Ontario.[8] The daily cost for stiripentol was calculated to be $40.54 based on the dosage of 50 mg/kg/day and using a patient weight of 31.8 kg (from STICLO trials).[2,3] Total daily treatment cost according to treatment regimens for stiripentol plus valproate plus clobazam versus valproate plus clobazam only was estimated to be $41.25

and $0.68 respectively. The annual treatment cost according to treatment regimen are presented in Table 2.

TABLE 2: ANNUAL TREATMENT COST ACCORDING TO TREATMENT REGIMEN

	Annual Treatment Cost (C$)
STP + VPA + CLB, Year 1	
NAC	$2,682.25
NSF	$15,056.47
SF	$15,056.47
STP + VPA + CLB, Years 2 to 5	
NAC	$247.97
NSF	$15,056.47
SF	$15,056.47
VPA + CLB, Years 1 to 5	
NAC	$247.97

Source: Manufacturer's Pharmacoeconomic Evaluation Report, Table 3, page 20.[8]
C$ = Canadian dollars; CLB = clobazam; NAC = not adequately controlled; NSF = not seizure free; SF = seizure free; STP = stiripentol; VPA = valproate.

2.2.3 Costs of Changing Therapy

The manufacturer's model assumes that patients on stiripentol plus valproate plus clobazam who are NAC after two months of treatment return to valproate plus clobazam only. The manufacturer reported that changing therapies is associated with health care costs; these costs, however, are not repeated in further model cycles. The calculation of resource use when epileptic therapy changes was based on NICE guidelines for economic evaluation in epilepsy.[6] The manufacturer reported that costs associated with medical visits were obtained from the Schedule of Benefits for Physician Services of the Ontario Health Insurance Plan (OHIP).[9] Resource use and costs associated with changing therapy are presented in Table 3.

TABLE 3: COST OF CHANGING THERAPY

	Number of Visits	Cost per Visit (C$)	Cost of Changing Therapy (C$)
General practitioner visit	1	$77.20	$77.20
Neurology outpatient initial visit	1	$176.35	$176.35
Neurology outpatient follow-up visit	2	$84.95	$169.90
Total			**$423.45**

C$ = Canadian dollars.
Source: Manufacturer's Pharmacoeconomic Evaluation Report, Table 4, page 21.[8]

2.2.4 Health Care Costs Associated With Seizure Status

The manufacturer reported that no detailed data on use of medical resources for the management of SMEI was available in the literature; therefore, probabilities of resource use as stated in the NICE guidelines for economic evaluation in epilepsy were used.[6] The manufacturer stated that the NICE guidelines did not distinguish between the NSF and NAC health states; therefore, the same use of

medical resources was attributed to both health states. Costs associated with health service use were obtained from the OHIP and Ontario Case Costing Initiative (OCCI).[10]

2.2.5 Health Care Costs Associated With Status Epilepticus

The manufacturer reported the probability of having SE episodes was taken from an open-label ME2080 study and was estimated at 10%.[11] The model assumes that 100% of patients experiencing SE will require emergency room visits and hospitalizations. The costs associated with SE episodes were obtained from the OCCI.[10]

2.2.6 Utilities

The manufacturer was unable to identify any published literature to provide the utility values for patients with SMEI. The manufacturer indicated that although the NICE epilepsy guidelines had reported utility values for epileptic children, the values were not specific to SMEI, a more severe form of epilepsy, and thus were assumed to underestimate the impact of SMEI on quality of life. In the model, the manufacturer used the utility values reported for Lennox-Gastaut syndrome, a form of epilepsy, which assumed comparability between the quality of life of SMEI and Lennox-Gastaut syndrome patients. This was confirmed by expert opinion according to the manufacturer, as well as by the clinical expert consulted by CDR for this review.

A literature search by the manufacturer found one study (published as an abstract and presented as a poster in a 2008 conference) that reported utility values for Lennox-Gastaut syndrome.[5] The study was conducted by interviewing 119 members of the general public and reported the utility values for four health states:

- Health State 1: uncontrolled disease, described as a frequency of 21 to 28 seizures per week (utility value of 0.393)
- Health State 2: a reduction of < 50% in seizure frequency (utility value of 0.461)
- Health State 3: a reduction of ≥ 50% and < 75% in seizure frequency (utility value of 0.605)
- Health State 4: a reduction of ≥ 75% in seizure frequency (utility value of 0.699).

The manufacturer indicated the health states reported in the study are not the same as the health states assumed for the economic model; therefore, the manufacturer assumed that patients in the NAC state are a mix of patients in Health State 1 and Health State 2, according to the state description (i.e., number of seizures per week). The manufacturer also assumed that patients in the SF state would have the same utility value as patients in Health State 4; this was based on the lack of reported utility with seizure-free health states. The utility values used in the model are presented in Table 4.

TABLE 4: UTILITY VALUES ASSOCIATED WITH THE MODEL'S HEALTH STATES

Model's Health States	Utility
SF	0.699
NSF	0.605
NAC	0.427
Death	0

Source: Manufacturer's Pharmacoeconomic Evaluation Report, Table 1, page 19.[8]
NAC = not adequately controlled; NSF = not seizure free; SF = seizure free.

2.2.7 Time Horizon

The model time horizon was set at five years using a cycle duration of one year.

2.2.8 Discounting

A discount rate of 5% was applied to both health and economic outcomes. A sensitivity analysis of the base-case scenario was conducted both with no discounting (discount rate of 0%) and a discount rate of 3%, as recommended by the CADTH guidelines.

2.2.9 Validation

The submitted economic evaluation indicated the Markov model used in this analysis was based on a recommendation in the NICE guidelines regarding economic evaluation in epilepsy.[6] As for internal validation, the manufacturer indicated this was confirmed by determining that the model responded logically to extreme parameter values.[8]

3. RESULTS

3.1 Manufacturer's Base Case

The modelled costs, life-years and QALYs are presented in Table 5. The incremental cost-utility ratio (ICUR) was $50,122 per QALY gained.

TABLE 5: RESULTS OF THE MANUFACTURER'S BASE CASE

	Costs ($)	Incremental costs ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
VPA + CLB	31,600	34,787	1.81	0.69	50,122
Stiripentol + VPA + CLB	66,388		2.51		

Source: Adapted from the Manufacturer's Pharmacoeconomic Evaluation Report, Table 8, page 26.[8]
CLB = clobazam; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; stiripentol = stiripentol; VPA = valproate.

3.2 Summary of Manufacturer's Sensitivity Analyses

3.2.1 One-Way Sensitivity Analyses

The manufacturer reported the results of deterministic sensitivity analyses on key model parameters that found the upper bound of the ICUR remained around the $50,000 threshold, indicating that the model predictions are stable and robust. The parameters for which uncertainty has the greatest impact on the incremental cost-effectiveness ratio are:

- Utility values for the health states: The manufacturer applied a ± 25% variation to the utility values. Using the lower-bound values, the ICUR increased to $113,913 per QALY gained.
- The response rates for SF patients compared with those NSF (i.e., responders) in the stiripentol plus valproate plus clobazam group. The manufacturer used the lower and upper bounds of the confidence interval (95% CI). Using the lower-bound values, the ICUR increased to $65,123 per QALY gained.
- Patient weight: Using the higher-bound values (36.2 kg in the stiripentol plus valproate plus clobazam group and 34.6 kg in the valproate plus clobazam group) resulted in the ICUR increasing to $58,994 per QALY gained. Of note, in the STICLO-France trial, at baseline, the interquartile range (IQR) for weight in the stiripentol group was 14 kg to 60 kg.

Many parameters for which there was considerable uncertainty were not varied in the manufacturer's one-way sensitivity analyses: time horizon, model cycle length, response rate in the valproate plus clobazam group, treatment cost in in the first year for patients in the NAC state, and potential waning of treatment effect throughout model duration.

3.2.2 Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was performed using Oracle Crystal Ball (version 11.1.1.1.00) by running the model 10,000 times using a triangular probability of distribution. The manufacturer reported that at a threshold of $50,000 per QALY, there is a 52.35% probability that the combination of stiripentol plus valproate plus clobazam is cost-effective. When a willing to pay threshold of $100,000 per QALY was used, the probability of stiripentol plus valproate plus clobazam being cost-effective increased to 98.4%. The manufacturer's PSA results reflect both high uncertainty and the sensitivity of the model to changes in the input parameters (i.e., 48% probability that the ICUR for stiripentol will exceed the $50,000 threshold). The manufacturer's PSA is also limited by the fact that some key parameters, as mentioned earlier, were not varied in the analysis; therefore, the PSA may not be accurately reflective of the uncertainty in this analysis.

3.3 CDR Analyses

Given the modest flexibility of the model, CDR was unable to undertake any sensitivity analyses surrounding the model time horizon or conduct a PSA to test the model based on some of the limitations. However, CDR was able to conduct a scenario analysis that assumed a therapeutic response in the valproate plus clobazam–only group. Additional CDR sensitivity analyses were conducted on patient weight, health state utilities, and assumptions for stiripentol costs in the first year of therapy for patients in the NAC state.

3.3.1 Scenario Analysis: Clinical Response in Valproate Plus Clobazam–Only Comparator Group

The manufacturer's base-case evaluation assumed that patients in the comparator group, using valproate plus clobazam only, do not display any response to the treatment, and therefore are only transitioning within the NAC health state. Based on clinical expert opinion, the assumption of no clinical response in the comparator group may be inappropriate as patients do exhibit a response although not significant enough to become SF. The CDR scenario analysis varied the percentage of patients in NSF (i.e., ≥ 50% to < 100% seizure control) using a range of 1% to 30% (manufacturer's base case: 0%). The results produced an ICUR range of $50,861 to $82,645 per QALY for stiripentol plus valproate plus clobazam.

3.3.2 Health States Utility Values

Utility values were based on a conference abstract from a study in Lennox-Gastaut syndrome (Verdian et al.[5] According to the clinical expert consulted for this review, Lennox-Gastaut syndrome is similar to Dravet syndrome. The Verdian study assessed the number of tonic-atonic seizures, whereas the STICLO study assessed the number of generalized tonic-clonic seizures.[12]In the Verdian study,[5] the uncontrolled health state was described as experiencing 21 to 28 seizures per week. This is much higher than the number of seizures reported at baseline in the STICLO-France trial (median of 4.5 per week, ranging from less than 1 to 17 per week).[3] It is therefore possible that the present utility associated with the NAC health state (0.427) is an underestimation of what would be expected for patients having the same characteristics and seizure type and frequency as those in the STICLO trials. CDR sensitivity analyses on the utility of the NAC health states were performed using the utility values from the Verdian study[5] (using the utility value of 0.461 from Health State 2 in Verdian for the value of the NAC state,

corresponding to 11 to 14 seizures per week, which is more similar to the number of seizures per week in STICLO). The CDR analyses also used utility values from the NICE guidelines using work done by Frew et al.[6,7] The authors looked into the cost-effectiveness of AEDs used as monotherapy and adjunctive therapy in the treatment of children with focal epilepsy. CDR analysis assumed the same utility increment from NAC to SF health states (0.135), considering that the manufacturer's model health states were based on the NICE guidelines. The CDR reanalyses produced an ICUR range of $58,614 to $120,419 per QALY.

3.3.3 Sensitivity Analysis: Patient Weight

The cost of treatment with stiripentol is based on the average weight of children included in the STICLO trials (mean of 32 kg).[2,3,8] Since no adjustment was made in the submitted model to take into account the weight gain expected when children grow, the cost of treatment considered in the analysis may be underestimated. The impact of weight increases was examined through CDR reanalyses that resulted in ICUR increases proportional to the increases in patient weight. Using a patient weight of 45 kg, the ICUR increased to $76,841 per QALY gained.

3.3.4 Duration of Treatment in Year 1 for Non-responders

The manufacturer assumed that patients on stiripentol plus valproate plus clobazam who were NAC after two months of treatment would return to receiving valproate plus clobazam alone.[2] This was assumed according to what was reported from the STICLO trials.[3] However, according to clinical expert opinion, SMEI patients are expected to receive stiripentol plus valproate plus clobazam for three to six months before clinical assessments are made to determine the efficacy of stiripentol. A CDR reanalysis calculated the cost of treatment for the first year to include four months of treatment with stiripentol instead of the two months of treatment assumed by the manufacturer. This analysis resulted in an ICUR of $51,160 per QALY gained.

3.3.5 "Most Likely Scenario"

A final CDR reanalysis was conducted wherein all the revised assumptions considered earlier were implemented.

- Clinical response of valproate plus clobazam alone: the percentage of patients in NSF (i.e., ≥ 50% to < 100% seizure control) was estimated at 10% (base case: 0%).
- The utility value for the NAC health state from the manufacturer data provided in Verdian et al. was used (i.e., 0.461 instead of 0.427 in the base case).[5]
- A patient weight of 45 kg was assumed (base case: 31.8 kg).
- Patients were assumed to receive stiripentol for a duration of four months in their first year (base case: two months).

Based on the above, the ICUR for stiripentol when added to valproate plus clobazam versus valproate plus clobazam alone increased from $50,122 to $104,491 per QALY gained.

a) Reanalysis Based on Price Reduction

Given the level of uncertainty in the results, and inability for CDR to modify structural parameters such as time horizon, a reanalysis was conducted presenting the ICUR for stiripentol when added to valproate plus clobazam (versus valproate plus clobazam alone), assuming price reduction scenarios for stiripentol. Results are very sensitive to price. Based on the manufacturer's submission, stiripentol, when added to valproate plus clobazam, would only dominate valproate plus clobazam with a price

reduction of 80% or more. Based on CDR's Most Likely Scenario analysis, the ICUR for stiripentol when added to valproate and clobazam would be less than $50,000 with a price reduction of around 50%.

TABLE 6: CDR ANALYSIS OF ICURS FOR STIRIPENTOL BASED ON VARIOUS PRICE REDUCTION SCENARIOS

Scenario	ICUR Based on Manufacturer's Analysis	Revised ICUR Based on CDR "Most Likely Scenario"
Manufacturer's base case	$50,122	$104,491
10% price reduction	$43,645	$92,364
20% price reduction	$37,167	$80,237
30% price reduction	$30,690	$68,110
40% price reduction	$24,212	$55,983
50% price reduction	$17,735	$43,856
60% price reduction	$11,258	$31,730
70% price reduction	$4,780	$19,603
80% price reduction	STP + VPA + CLB dominant	$7,476
90% price reduction	STP + VPA + CLB dominant	STP + VPA + CLB dominant

CDR = Common Drug Review; CLB = clobazam; dominant = more efficacy at a lower cost than comparator; ICUR = incremental cost-utility ratio; STP = stiripentol; VPA = valproate.

4. DISCUSSION

4.1 Key Limitations

The limitations identified with the submitted economic evaluation pertain to the structure and parameters used in the model. The overall data are limited for this analysis; treatment effects for a chronic disease that are based on small clinical trials with very short durations (two months) require assumptions about the treatment effects beyond trial duration. The model structure does not facilitate varying the model's cycle length or time horizon. In addition, the model does not adjust for the expected weigh increases that are inherent with patient growth over the model time horizon, nor does it allow for consideration of possible waning treatment effects over time. Due to limited available data to inform this analysis, several assumptions were required, thus generating a high level of uncertainty in the results.

4.1.1 The Modelling and Assumptions Surrounding Clinical Response in the Model

In the submitted Markov model, the manufacturer assumed that all patients in the comparator group (i.e., treated with valproate plus clobazam alone) are in the NAC state (< 50% reduction in seizure frequency) and can transition only to the death state.[8] According to clinical expert opinion, SMEI patients on valproate plus clobazam alone do respond to treatment and will experience seizure control; however, the response will not be sufficient to render them SF. STICLO-France showed that 5% of patients (9.1% in STICLO-Italy) in the valproate plus clobazam–alone group achieved a reduction of at least 50% in the number of seizure episodes.

4.1.2 Health States Utility Values

There is considerable uncertainty around the health state utilities used in this model. Utility values were derived from an abstract that described the elicitation of preferences for health states associated with Lennox-Gastaut syndrome, an epileptic encephalopathy with comparable presentation that was confirmed by clinical experts.[5] The abstract's description of the health states (the full study has not been published) does not correspond to the number and type of seizures at baseline in the STICLO trials. The

anchor state (Health State 1 [HS-1]) for uncontrolled disease was described in the model as a frequency of 21 to 28 seizures per week, versus 18 seizures per *month* in STICLO (i.e., NAC health state), and the model was comprised of four health states (versus three health states in the economic analysis).[3,5] Results from CDR sensitivity analyses on utility values confirm the model's sensitivity to changes in utility values in the NAC health state.

4.1.3 Treatment Effects

The treatment effects for stiripentol plus valproate plus clobazam were based on efficacy results observed at two months in the STICLO trials.[3] These effects at two months were extrapolated for the duration of the model's time horizon of five years.[2] This assumption implies that patients will carry the antiepileptic effects of stiripentol beyond the two-month treatment period throughout the rest of the model time horizon. This assumption biases the model results in favour of stiripentol. Longer-term data tend to show that despite a complete response to treatment in two months, there is a chance these patients may suffer other crises,[3,13] which may reduce the expected QALY gains with stiripentol and ultimately increase the ICUR. The failure of the analysis to consider the possible waning of treatment effects was not addressed; the impact of this on the study results is therefore unknown.

Additional key limitations are listed in Table 7.

TABLE 7: OTHER LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Cycle length of one year with model time horizon of five years.	Clinical expert opinion indicated that patients' treatment regimens are expected to change more frequently than at one-year intervals. The clinical expert also stated that the expected treatment duration can last up to 15 years. The submitted model did not facilitate the variation of cycle length or time horizon.	Increases uncertainty in the results.
Patient weight remains constant throughout model time horizon.	The model does not adjust for the expected weigh increases that are inherent with patient growth over a five-year time horizon.	The incremental cost of stiripentol + valproate + clobazam compared with valproate + clobazam was likely underestimated.
AEs were considered negligible and were not included in the model.	The STICLO trials indicated a higher probability of experiencing side effects in patients using stiripentol. The costs associated with the management of adverse effects were not included. Disutilities associated with AEs were not included either.	Increases uncertainty in the results; however, most common AEs generally respond to dose reduction. Attributing cost to some AEs may prove to be difficult, e.g., cost of somnolence or cost of loss of appetite.

AE = adverse event.

4.2 Issues for Consideration

4.2.1 Clinical Practice

Clinical expert opinion indicated that treatment for SMEI involves varying treatments that can range from constantly changing doses of one or more treatments to including additional agents, to the present treatment regimen. Such variation in treatment practices is expected to have various implications on the overall costs and effects associated with stiripentol use in SMEI patients. The clinical expert also stated that the dosing of clobazam may reach a maximum of 1 mg/kg daily in clinical practice if added to valproate (without stiripentol). This is higher than the maximum dose of 0.5 mg/kg daily of clobazam if used with stiripentol and valproate; therefore, a higher response rate might be expected for valproate plus clobazam in clinical practice than what was observed in the STICLO trials.[2,3]

4.2.2 Off-Label or Expanded Use

There is concern that stiripentol will be prescribed and administered to patients who may already be responding adequately to valproate plus clobazam alone or to other antiepileptic drugs. Expert opinion indicates that adding stiripentol to the existing valproate plus clobazam combination will be driven by the desire to increase seizure control and reduce, through dose reductions, the incidence of adverse events caused by valproate plus clobazam.

4.3 Patient Input

Patient input for stiripentol was provided by Dravet.ca, the Canadian network for families, friends, and caregivers of people with Dravet spectrum disorders. The patient group stated that Dravet syndrome is associated with frequent seizures, multiple seizure types, prolonged seizures, and episodes of life-threatening SE. The manufacturer's economic evaluation takes into account the costs and outcomes associated with seizures and SE.

5. CONCLUSIONS

A number of limitations with the manufacturer's economic submission were identified. When accounting for them, CDR found the ICUR for stiripentol compared with valproate plus clobazam ranged from $51,160 to $120,419 per QALY gained, with a most likely ICUR estimate of $104,491 per QALY gained.

APPENDIX 1: COST COMPARISON TABLE

The comparators presented in the table below have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 8: COST COMPARISON TABLE FOR COMPARATORS FOR DRAVET SYNDROME

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Dose[a]	Daily Cost[b] ($)	Annual Cost[b] ($)
Stiripentol (Diacomit)	**250 mg 500 mg**	**Capsule or powder for suspension**	**6.3667[c] 12.7333[c]**	**50 mg/kg/day in 2 to 3 divided doses**	**38.20**	**13,943**
Clobazam (generics)	10 mg	Tablet	0.1098	0.5mg to 40 mg daily	0.01–0.44	20–160
				0.5 mg/kg/day when combined with stiripentol for Dravet syndrome	0.16	58.40
				Up to 1 mg/kg/day (max. 40 mg) when not used with stiripentol	0.33	120.45
Levetiracetam (generics)	250 mg 500 mg 750 mg	Film-coated tablet	0.8000[d] 0.9750[d] 1.3500[d]	40 to 100 mg/kg/day to a maximum of 3,000 mg	2.75–5.40	1,004–1,971
Topiramate (generics)	25 mg 100 mg 200 mg	Film-coated tablet	0.3128 0.5929 0.8854	5 to 15 mg/kg/day in 2 divided doses	1.22–2.40	445–875
Valproic acid (generics)	250 mg 500 mg 50 mg/mL	Enteric-coated tablet Enteric-coated tablet Syrup	0.1366 0.4125 0.0398	15 to 60 mg/kg/day in divided doses titrated to therapeutic levels from serum	0.27–0.96 0.36–1.43	100–350 131–523

All prices from Ontario Drug Benefits Formulary (May 2014) unless otherwise indicated. Dose ranges taken from Health Canada product monographs or consultation with a clinical expert.

[a] The expert indicated that most patients with Dravet syndrome will be at or near the maximum dose.

[b] Costing based on a 30 kg patient.

[c] Manufacturer's submitted price.

[d] Saskatchewan Drug Plan Formulary (May 2014).

APPENDIX 2: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

Three health technology assessment bodies have published appraisals of stiripentol in this indication: Scotland (SMC) and Wales (AWMSG) in 2008 and, more recently, Quebec (INESSS, June 2014).

The submissions to the SMC and AWMSG did not include a formal economic evaluation. The economic evidence submitted was not sufficient to assess the cost-effectiveness of stiripentol.

A summary of the Institut national d'excellence en santé et en services sociaux (INESSS) submission and recommendation is provided in the following table.

TABLE 9: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	INESSS (June 2014)
Drug	Stiripentol in conjunction with valproate and clobazam
Price	$1,146 per year for a 30 kg patient $2,673 per year for a 70 kg patient (Formulary price of $6.37 per 250 mg capsule; $12.73 per 500 mg capsule)
Comparator	Valproate and clobazam alone
Population modelled	Patients with SMEI (Dravet syndrome) whose seizures are not adequately controlled with valproate and clobazam
Time horizon	5 years
Discount rate	Not reported
Study question	Estimate ICUR of stiripentol + valproate + clobazam vs. valproate + clobazam alone for patients with Dravet syndrome
Type of model	Cost-utility model
Key outcomes	QALYs
Results	Manufacturer: • Base case: $50,069 per QALY (ministry of health perspective); dominant (societal perspective) • DSA: dominant to $113,791 per QALY (ministry of health or societal perspective) • PSA: CEAC indicated 100% ICUR < $50,000 and 100% ICUR < $100,000 (societal perspective) INESSS reanalyses: • Dominant to $67,000 per QALY
Sources of uncertainty	Patient weight, long-term efficacy, adverse events
Recommendations	• Recommended, in association with valproate and clobazam, for treatment of patients with Dravet syndrome whose seizures are not adequately controlled with valproate and clobazam • The initial authorization is granted for a maximum period of 4 months • The authorization will be renewed if it is shown that the treatment has reduced the monthly frequency of generalized seizures about 50% • Subsequent approvals will be for maximum periods of 12 months

	INESSS (June 2014)
CDR assessment	• INESSS appears to have received a similar submission to that of CDR; similar limitations were noted: lack of long-term data, assumption that response at 2 months is maintained over 5 years, and lack of consideration of patient weight gain over time.

CDR = Common Drug Review; CEAC = cost-effectiveness acceptability curve; CUA = cost-utility analysis; DSA = deterministic sensitivity analyses; ICUR = incremental cost-utility ratio; HTA = Health Technology Assessment; INESSS = Institut national d'excellence en santé et en services sociaux; LY = life-year; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; SA = sensitivity analysis; vs. = versus.

APPENDIX 3: SUMMARY OF KEY OUTCOMES

TABLE 10: SUMMARY ASSESSMENT OF STIRIPENTOL AS AN ADJUNCT TO VALPROATE AND CLOBAZAM COMPARED WITH VALPROATE AND CLOBAZAM ALONE

Stiripentol + valproate and clobazam versus valproate and clobazam	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Manufacturer's base case: $50,122 per QALY					

CE = cost-effectiveness; QALY = quality-adjusted life-year; NA = not applicable.

APPENDIX 4: ADDITIONAL INFORMATION

TABLE 11: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	The model also did not provide the actual PSA model; only the PSA results were submitted.		
Was the material included (content) sufficient?		X	
Comments	The submitted model did not allow modification of analysis time horizon nor did it adjust for incremental weight gain of patients over the time horizon.		
Was the submission well organized and was information easy to locate?	X		
Comments			

TABLE 12: AUTHOR INFORMATION

Authors	Affiliations
Jean Lachaine Veronique Lambert-Obry	PeriPharm Inc.

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

Note: No documentation was provided regarding author agreement with the submitted documents or control over the methods.

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