Common Drug Review
Clinical Review Report

April 2015

Drug	stiripentol (Diacomit) (capsule and powder for suspension, 250 mg and 500mg)
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

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ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	alanine transaminase
AST	aspartate aminotransferase
CI	confidence interval
CLO	clobazam
DB	double blind
HRQoL	health-related quality of life
ITT	intention to treat
NICE	National Institute for Health and Care Excellence
PL	placebo
PP	per protocol
RD	risk difference
SAE	serious adverse event
SCN1A	sodium channel alpha-1 subunit gene
SD	standard deviation
SMEI	severe myoclonic epilepsy in infancy
STP	stiripentol
VPA	valproate
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Severe myoclonic epilepsy in infancy (SMEI), also known as Dravet syndrome, is a rare disorder with an incidence ranging from 1 per 20,000 to 1 per 40,000. Dravet syndrome is one of the most drug-resistant forms of epilepsy. It is estimated that 10 to 20 new cases of Dravet syndrome are diagnosed yearly in Canada. This is a refractory form of epilepsy, which is characterized by febrile or afebrile, prolonged, generalized clonic or tonic-clonic seizures starting in the first year of life. Mental retardation and behavioural disorders usually present after age of two, and the seizures have a deleterious effect on cognitive development. Dravet syndrome is associated with poor psychomotor development and a high mortality rate in patients' early life. The diagnosis of Dravet syndrome is based primarily on clinical observations of tonic-clonic seizures during the first year of life, the occurrence of myoclonic seizures and ataxia later, impaired psychomotor development following the onset of seizures, and poor response to antiepileptic drugs. Mutations in the sodium channel alpha-1 subunit (*SCN1A*) gene have been identified in approximately 70% to 80% of patients with Dravet syndrome. Valproate, clobazam, topiramate, and levetiracetam are used as pharmacological treatment for this disorder in children.

Stiripentol (Diacomit) was approved by Health Canada in 2012 for adjunctive therapy of Dravet syndrome as described in the following table. Stiripentol is available in 250 mg or 500 mg capsules or powder for suspension; the Health Canada–recommended dose is 50 mg/kg/day, which may be divided into two to three doses per day.

Indication under review
Use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy whose seizures are not adequately controlled with clobazam and valproate alone.
Listing criteria requested by sponsor
As per indication

The objective of this review was to perform a systematic review of the beneficial and harmful effects of stiripentol 250 mg and 500 mg as adjunctive therapy for refractory generalized tonic-clonic seizures in patients with SMEI (Dravet syndrome).

Results and Interpretation

Included Studies

Two multi-centre, randomized, parallel-group, double-blind, placebo-controlled studies, STICLO-France (N = 42) and STICLO-Italy (N = 23), met the inclusion criteria for this systematic review. The two studies employed similar study designs to compare the efficacy and safety of stiripentol with placebo in patients aged 3 to 18 years old with a diagnosis of Dravet syndrome who were being treated concomitantly with clobazam and valproate. Both studies included a one-month baseline period in which patients received stable doses of clobazam (0.5 mg/kg/day, maximum 20 mg/day) and valproate (30 mg/kg/day), and a two-month double-blind period (when stiripentol was administered orally at a dose of 50 mg/kg/day in combination with clobazam and valproate), followed by one month of open-label stiripentol therapy (plus clobazam and valproate) for all study participants. During the double-blind period, the doses of

clobazam or valproate were to be reduced in the event of serious adverse events: poor appetite or persistent weight loss for valproate, and drowsiness or hyperexcitability for clobazam.

The primary outcome measure was the proportion of responders during the double-blind period. Children were considered responders when they did not fall into any of the following non-responder categories:

- failed to achieve at least a 50% decrease in the number of generalized clonic or tonic-clonic seizures during the second month of the double-blind period, compared with baseline
- withdrawn due to status epilepticus
- experienced a more than 50% increase in number of seizures compared with baseline within 0 to 20 days following entry into the double-blind period
- experienced more than a 50% increase in the number of seizures during the baseline period (compared with the previous period), and did not return to the previous number before the baseline period during the first month of the double-blind period. All the seizure outcomes measured in the STICLO-France and STICLO-Italy studies referred to generalized clonic or tonic-clonic seizures.

According to the clinical expert consulted for this review, the study populations were similar to the patients with Dravet syndrome who would be seen in Canadian clinics, however, the dose of co-administered clobazam was lower than would be used in clinical practice (a maximum dose of 20 mg/day adopted in the two studies versus 40 mg/day recommended by Health Canada for children aged 2 to 16 years). The Health Canada reviewers' report indicated the lower clobazam dosage in the STICLO studies was acceptable because the dose adjustment was done for safety and tolerability reasons and represented the real-life use of clobazam in conjunction with stiripentol; in addition, analysis of individual patient data by Health Canada suggested the suboptimal dose of clobazam did not result in increased seizure frequency during the baseline period, which could have exaggerated the effect of stiripentol during the double-blind period. However, the findings from this analysis were generated from a small number of patients; therefore; the impact of change in clobazam dosage on seizure control was not conclusive. In addition, the relatively low dose of clobazam in the placebo group may still be suboptimal and patients in the placebo group may not be representative of how patients are treated in clinical practice.

Efficacy

In general, compared with the placebo group, patients treated with stiripentol 50 mg/kg/day had a lower frequency of seizures (Table 1). Nine (45%) stiripentol-treated patients in STICLO-France and three (27%) in STICLO-Italy reported no seizures during the second month of the double-blind period, while in the placebo groups, all patients still experienced at least one episode of clonic or tonic-clonic seizures. The proportion of responders was the primary outcome measure in both studies. In both studies, the percentage of responders was statistically significantly higher in the stiripentol groups compared with placebo: 71.4% versus 5.0%, and 66.7% versus 9.1% in STICLO-France versus STICLO-Italy, respectively. The pooled risk difference for the proportion of responders was 0.61, with 95% confidence intervals ranging from 0.43 to 0.79. In both studies, the percentage of children with at least a 50% decrease in seizures during the second month of the double-blind period was higher in the stiripentol groups compared with placebo: 71.4% versus 5.0% ($P < 0.00002$) and 66.7% versus 9.1% (P value not reported) in STICLO-France versus STICLO-Italy respectively. Compared with placebo, patients treated with stiripentol reported greater reductions from baseline in the mean number of seizures during the first and second months of the double-blind period in both studies; the between-treatment differences were statistically significant, excepting those from the second month of STICLO-Italy.

While both studies consistently reported a decrease in seizure frequency with stiripentol versus placebo, the benefit of stiripentol may be overestimated due to a known pharmacokinetic drug–drug interaction of stiripentol. Stiripentol inhibits several cytochrome P450 isoenzymes. This leads to pharmacokinetic interactions with numerous drugs, including co-administered antiepileptics. In the included studies, plasma levels of norclobazam (an active metabolite of clobazam) during the double-blind period were noticeably elevated over baseline levels in the stiripentol groups, but not the placebo groups. The combination of the relatively low dose of clobazam used, plus the pharmacokinetic drug–drug interaction that elevated levels of norclobazam in the stiripentol groups, may have overestimated the benefit of stiripentol.

In both STICLO-France and STICLO-Italy, the seizure frequency was recorded by patient's parents or caregivers on a diary. However, accurate identification, differential diagnosis, and reliable recording of seizure frequency can be very challenging, especially in children. A retrospective study examining the accuracy of caregiver reporting of any seizure types in children with epilepsy found the sensitivity of seizure identification by parents was only 43.1%. While it may be difficult to accurately count seizures, and although the need for "proxy reporting" by parents or caregivers adds uncertainty as to the validity of the information reported, these studies focused on generalized clonic or tonic-clonic seizures, which are expected to be easy to identify.

Finally, the available randomized controlled trial evidence is limited by the short duration of the trials (which do not provide evidence of efficacy beyond two months), and the lack of data on other outcomes of interest, including health care utilization, and health-related quality of life.

Harms

In both included studies, adverse events were higher in the stiripentol group compared with the placebo group and were reported as being mild or moderate in severity: the percentage of patients reporting adverse events in the stiripentol groups ranged from 83% to 100%, compared with 27% to 45% in the placebo groups. The most frequently reported adverse events were drowsiness, behavioural disorders, gastrointestinal disorders, and neurological disorders. Both studies reported a higher percentage of patients with appetite loss and weight loss in the stiripentol groups than the placebo groups. In the STICLO-Italy study, safety data regarding serious adverse events were not explicitly reported. In STICLO-France, patients in the stiripentol group reported more serious adverse events compared with the placebo group.

Elevated plasma levels of norclobazam in the stiripentol groups may explain the higher incidence of adverse events in these groups. In STICLO-France and STICLO-Italy, doses of valproate and clobazam were to be decreased in cases of serious adverse events. In STICLO-France, compared with placebo, more patients in the stiripentol group required dose reductions; however, the study report did not specify the percentage of patients that required dose reductions for each drug separately (clobazam and valproate). Since stiripentol was administered in conjunction with clobazam and valproate, it is not possible to discern adverse events that may be specifically attributed to stiripentol. Finally, given the short duration of the studies, there is limited evidence of long-term safety, and the small sample sizes preclude the identification of infrequent or rare adverse events.

Pharmacoeconomic Summary

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis of stiripentol as adjunct to clobazam and valproate in patients with SMEI (Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate alone. The analysis was based on a Markov model over a five-year time horizon. The model comprised four health states: not adequately controlled (NAC), not seizure free (NSF), seizure free (SF), and death. NAC was defined as < 50% reduction in seizure frequency from baseline, whereas NSF was 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. Probabilities of transition from NAC, NSF, and SF to death were derived from the results of the DIAVEY study, a stiripentol post-marketing non-interventional study. 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. Utility values were obtained from a study reporting utility values for Lennox-Gastaut syndrome; a form of epileptic encephalopathy that the manufacturer stated is comparable to SMEI.

Results of Manufacturer's Analysis

The manufacturer reports that the incremental cost per quality-adjusted life-year (QALY) for stiripentol plus clobazam and valproate therapy was $50,122 compared with clobazam and valproate alone.

Interpretations and Key Limitations

The model assumed that patients on clobazam and valproate alone would not show any response to treatment, which is inconsistent with the findings of the STICLO trials, in which 5.0% to 9.1% of patients showed a reduction of at least 50% in the number of seizure episodes. The health-state utilities used in the model may be lower than what would be expected for patients having the same characteristics and seizure frequency as those in the STICLO trials. Further, because the model did not consider the weight gain inherent in patient's growth over the model's time horizon, the incremental cost of stiripentol is underestimated. The model also did not consider the potential waning of treatment effect and assumed the efficacy of stiripentol observed at two months is maintained over five years. The submitted model did not allow Common Drug Review (CDR) reanalyses on the impact of structural uncertainty on model results (e.g., time horizon and cycle length), which further increases uncertainty around the manufacturer's results.

Results of CDR Analysis

CDR reanalyses on the aforementioned limitations produced incremental cost-utility ratios (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 patient weight and the percentages of patients responding to valproate plus clobazam therapy alone. In a CDR analysis on the most likely scenario based on the limitations and assumptions identified 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.

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.

Conclusions

Based on a systematic review of two double-blind RCTs, compared with placebo, adjunctive therapy with stiripentol 50 mg/kg/day (added on to clobazam and valproate) resulted in statistically significantly reduced seizure frequency and higher percentage of responders among pediatric patients with Dravet syndrome over two months. However, the combination of the relatively low dose of clobazam used, plus a pharmacokinetic drug–drug interaction that resulted in elevated levels of norclobazam in the stiripentol groups but not the placebo groups, may have overestimated the benefit of stiripentol.

Adverse events and serious adverse events occurred more frequently in stiripentol-treated patients compared with placebo. Drowsiness, sleepiness, appetite loss, weight loss, and hyperexcitability were the most common complaints from patients receiving stiripentol. The elevated levels of norclobazam in stiripentol-treated patients may have contributed to the higher frequency of adverse events. Since stiripentol was administered in conjunction with clobazam and valproate, it is not possible to discern adverse events that may be specifically attributed to stiripentol.

Finally, given the short duration of the studies, there is limited evidence of long-term efficacy and safety and no there is a lack of data on other outcomes of interest such as health-related quality of life and health care utilization.

TABLE 1: SUMMARY OF RESULTS

	STICLO-France		STICLO-Italy	
	STP (N = 22)	PL (N = 20)	STP (N = 12)	PL (N = 11)
Seizure-free status during the second month of DB period				
n/N (%)	9/20 (45)	0/16	3/11 (27)	0/9
P value (STP vs. PL)	NR		NR	
Proportion of responders				
n/N (%)	15/21 (71.4)	1/20 (5.0)	8/12 (66.7)	1/11 (9.1)
Between-group difference and 95% CI, STP vs. PL (%)	66.4[a] (42.2 to 85.7)		57.6[a] (95% CI NR)	
P value (STP vs. PL)	< 0.00002		0.009	
Percentage of children with ≥ 50% decrease in seizures during the second month of DB period				
n/N (%)	15/21 (71.4)	1/20 (5.0)	8/11 (73)	1/9 (11)
P value (STP vs. PL)	< 0.00002		NR	
Number of tonic-clonic seizures in first month of DB period vs. baseline, mean (SD)				
Baseline	17.9 (17.3)	18.5 (17.0)	33.6 (28.2)	27.4 (28.6)
First month	2.72 (4.06) (n = 21)	23.82 (36.55) (n = 20)	4.7 (7.3) (n = 12)	29.0 (35.6) (n = 11)
P value for change from baseline (STP vs. PL)[b]	< 0.001		< 0.05	
Number of tonic-clonic seizures in second month of DB period vs. baseline, mean (SD)[c]				
Baseline	17.9 (17.3)	18.5 (17.0)	33.6 (28.2)	27.4 (28.6)
Second month	5.15 (7.73) (n = 20)	13.80 (7.33) (n = 16)	9.8 (10.0) (n = 11[d])	16.7 (11.3) (n = 9[d])
P value for change from baseline (STP vs. PL)[b]	< 0.002		NS	
Death				
n (%)	0	0	0	0
AEs				
Patients with > 0 AEs, N (%)	21 (100)	9 (45)	10 (83)	3 (27)

	STICLO-France		STICLO-Italy	
	STP (N = 22)	PL (N = 20)	STP (N = 12)	PL (N = 11)
SAEs				
Patients with > 0 SAEs, N (%)	6 (28.6)	3 (15)	0	0
WDAEs				
WDAEs, N (%)	1 (4.8)	2 (10)	1 (8.3)	0

AE = adverse event; CI = confidence interval; DB = double-blind; NR = not reported; NS = non-significant; PL = placebo; SAE = serious adverse event; SD = standard deviation; STP = stiripentol; vs. = versus; WDAE = withdrawal due to adverse event.
[a] Calculated by CDR.
[b] The *P* value was reported in the manufacturer analysis using Mann-Whitney test.
[c] The mean number of seizures and related variation during the second month of the double-blind period compared with baseline were calculated in patients who had completed the study.
[d] Per-protocol population data.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Severe myoclonic epilepsy in infancy (SMEI), also known as Dravet syndrome, is a rare disorder with an incidence ranging from 1 per 20,000 to 1 per 40,000.[1,2] Disease incidence for the Canadian population is not available, however, it is estimated there are 10 to 20 new cases of Dravet syndrome per year in Canada.[3] This is a refractory form of epilepsy, which is characterized by febrile or afebrile, prolonged, generalized clonic or tonic-clonic seizures starting in the first year of life. Generalized tonic-clonic seizures (also called grand mal seizures) are caused by abnormal electrical activity throughout the brain and are characterized by two consecutive stages: tonic stiffening following by clonic flexion motions. They may cause laboured respirations, cyanosis, incontinence, involuntary tongue biting, and loss of consciousness.[4,5] Mental retardation and behavioural disorders usually present after the age of two, and the seizures have a deleterious effect on cognitive development.[6] Dravet syndrome is associated with poor psychomotor development and a high mortality rate in patients' early life (ranging from 14.3% to 20.8% in case series, including pediatric and adult patients).[1,7,8] The main causes of death included status epilepticus and its consequences in the younger patients, and sudden unexpected death in both older children and those beyond the pediatric age.[8]

The diagnosis of Dravet syndrome is based primarily on clinical observations of tonic-clonic seizures during the first year of life, the occurrence of myoclonic seizures and ataxia later, impaired psychomotor development following the onset of seizures, and poor response to antiepileptic drugs.[9] Mutations in the sodium channel alpha-1 subunit (*SCN1A*) gene have been identified in approximately 70% to 80% of patients with Dravet syndrome.[7] Most of these mutations are "de novo" (not inherited from the parents), while familial *SCN1A* mutations occur as well.[1] Confirmatory genetic testing for *SCN1A* in patients with suspected Dravet syndrome, especially those younger than two years of age (in whom a clinical diagnosis can be difficult), has been shown to decrease unnecessary testing and improve access to therapies and supportive-care services for families.[7]

1.2 Standards of Therapy

Seizures are one of the typical clinical manifestations in patients with Dravet syndrome, and the magnitude of mental deterioration can be related to the frequency of seizures.[10] According to the clinical expert consulted for this review, a major treatment goal in this population is to reduce seizures with the highest morbidity, such as status epilepticus. However, Dravet syndrome is one of the most drug-resistant forms of epilepsy.[10]

There are no clinical practice guidelines in North America that provide guidance on the treatment of Dravet syndrome. In a clinical practice guideline developed by the National Institute for Health and Care Excellence (NICE), valproate or topiramate monotherapy is recommended as the first-line pharmacological treatment of Dravet syndrome in children.[11] If the first-line therapy is ineffective or not tolerable, clobazam or stiripentol may be added as adjunctive treatment. The clinical effectiveness of topiramate or levetiracetam as add-on therapy (i.e., added to existing antiepileptic drugs such as clobazam, lamotrigine, vigabatrin, phenobarbital, clonazepam, and stiripentol) for reducing seizure frequency has been observed in small open-label, uncontrolled studies of children with Dravet syndrome (APPENDIX 5: EFFICACY AND SAFETY EVIDENCE FOR LEVETIRACETAM AND TOPIRAMATE IN THE TREATMENT OF DRAVET SYNDROME). The efficacy of a ketogenic diet was reported in observational studies. Patients with drug-resistant disease usually require a combination of antiepileptic drugs. Evidence from

controlled trials of ketogenic diets is limited, given the difficulty of performing such trials for a rare and severe disorder.[10]
Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin should be avoided in the target population due to increased seizure activity or other neurologic worsening associated with the use of these drugs.[7,11,12]

1.3 Drug

Stiripentol (Diacomit) is a derivative of alpha-ethylene alcohol. Its antiepileptic effect stems from moderating the gamma-aminobutyric acid (GABA)ergic system, and inhibiting several isoenzymes (in particular the cytochrome P450 system) involved in the hepatic metabolism of other antiepileptic drugs, thus potentiating their effects.[12-14]

Stiripentol was granted orphan drug status at the European Medical Agency in 2000, and was registered as an orphan drug in January 2007 in Europe for Dravet syndrome as adjunctive therapy with valproate and clobazam.[12] In December 2012, stiripentol was approved by Health Canada for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with Dravet syndrome whose seizures are not adequately controlled with clobazam and valproate alone.[15]

Stiripentol is available as 250 mg or 500 mg capsules or powder for suspension. The Health Canada–recommended dose is 50 mg/kg/day, which may be divided into two to three doses per day.[14]

Indication under review
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 criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF STIRIPENTOL, CLOBAZAM, AND VALPROATE

	Stiripentol	Clobazam	Valproate
Mechanism of Action	Anticonvulsant properties; has the ability to inhibit cytochrome P450 system and involved in the hepatic metabolism of other AEDs; modulation of the GABAergic system	1,5-benzodiazepine with anticonvulsant properties; modifications to the function of GABA	Blocks voltage-dependent Na+ channels and increases brain levels of GABA
Indication[a]	Use in conjunction with CLO and VPA as adjunctive therapy of Dravet syndrome where seizures are not adequately controlled	Adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anticonvulsant therapy	Generalized epilepsy (primary); partial epilepsy (either alone or as adjuvant therapy); mania (where other therapy has proved inadequate or is inappropriate)

	Stiripentol	Clobazam	Valproate
	with CLO and VPA alone		
Route of Administration	PO		
Recommended Dose	Upward dose escalation over 3 days to reach 50 mg/kg/day; the daily dosage may be administered in 2 or 3 divided doses For children younger than 3 years of age, the decision for use of this drug needs to be made on an individual patient basis, taking into account the potential clinical benefits and risks; adjunctive therapy with STP should be started only when the diagnosis of DS has been clinically confirmed	Infants (< 2 years): initial daily dose is 0.5 mg/ kg/day 1 mg/kg/day Children (2–16 years): initial dose is 5 mg/day; may be increased at 5-day intervals to a max of 40 mg/day Adults: starting at 5 mg/day to 15 mg/day, gradually increasing to a max daily dose of 80 mg, as necessary	May take several days or weeks to show an initial effect; may be given twice daily **Monotherapy for epilepsy:** Adults: start with 600 mg/day increasing by 200 mg/day at 3-day intervals until control is achieved Children > 20 kg: initial dosage 400 mg/day, irrespective of weight — within the range of 20–30 mg/kg/day Children < 20 kg: 20 mg/kg/day. When > 40 mg/kg/day, clinical chemistry and hematological parameters should be monitored **Combined therapy for epilepsy:** Dose may be increased by 5–10 mg/kg/day when used with anticonvulsants, which induce liver enzyme activity
Serious Side Effects/Safety Issues	The dose of VPA and CLO might need to be adjusted when STP is co-administered; rare cases of delirium and hallucinations have been reported in adult patients taking STP; patients with past history of psychosis in the form of episodes of delirium should be monitored closely	For elderly, debilitated patients and those with organic brain disorders, start at the lowest possible dose; possible additive effects if combined with alcohol or drugs with CNS-depressant effects; physical and psychological dependence are known in patients taking benzodiazepines; abrupt discontinuation after prolonged use should be avoided; dosage must be adjusted when co-administered with other AEDs	Cases of life-threatening pancreatitis have been reported; severe liver damage; increases the risk of prolonged bleeding time during surgery, and suicidal behaviour Interactions with other medicines such as AEDs, anticoagulants, oral contraceptives, psychotropic drugs, and alcohol

AED = antiepileptic drug; CLO = clobazam; CNS = central nervous system; DS = Dravet syndrome; GABA = gamma-aminobutyric acid; max = maximum; Na+ = sodium ion; PO = oral; STP = stiripentol; VPA = valproate.

[a] Health Canada indication.

Sources: Product monographs for stiripentol,[14] clobazam,[16] and valproate.[17]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of stiripentol (Diacomit) 250 mg and 500 mg as adjunctive therapy for refractory generalized tonic-clonic seizures in patients with SMEI (Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate alone.

2.2 Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR, supporting the Health Canada indication of interest (Dravet syndrome), as well as those meeting the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with SMEI whose seizures are not adequately controlled with clobazam and valproate alone. Subgroups: • age groups • seizure types (clonic and tonic-clonic seizures vs. other seizures) • *SCN1A* mutation (positive vs. negative)
Intervention	Stiripentol 50 mg/kg/day orally in 2 or 3 divided doses daily in conjunction with clobazam and valproate
Comparators	Alone or in combination: Valproate Clobazam Topiramate Levetiracetam Placebo Ketogenic diet
Outcomes	**Key efficacy outcomes:** • Seizure-free status (data by seizure type if available) • Reduction in seizure frequency: e.g., time to reduction in seizure frequency or proportion of responders (achievement of ≥ 50% or ≥ 75% reduction in seizure frequency from baseline) • Reduction in episodes of status epilepticus • HRQoL evaluated by a validated instrument • Death (all-cause and sudden unexplained death in epilepsy) **Other efficacy outcomes:** • Health care utilization (physician visits, emergency room visits, hospitalization, etc.) • Psychomotor retardation or ataxia evaluated by validated scales **Harms outcomes:** AEs, SAEs, WDAEs, harms of special interest (e.g., loss of appetite, drowsiness, psychiatric-related events, seizures related to rapid withdrawal, elevated transaminases, and neutropenia)
Study Design	Published and unpublished RCTs

AE = adverse event; AED = antiepileptic drug; DB = double blind; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; *SCN1A* = sodium channel, voltage-gated, type I, alpha subunit; SMEI = severe myoclonic epilepsy in infancy; vs = versus; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concept was Diacomit (stiripentol). No methodological filters were applied. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language.

The initial search was completed on April 24, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on September 17, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contact with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

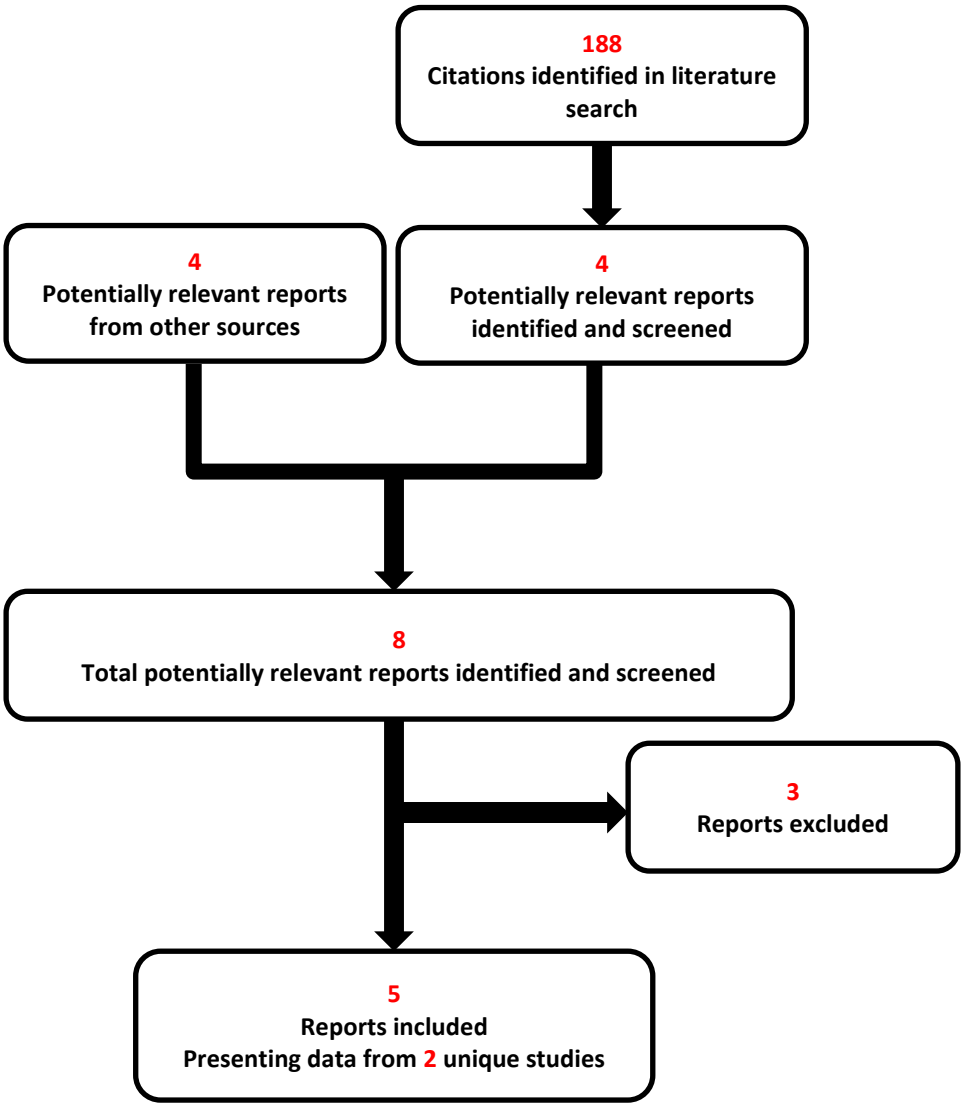
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4 excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES. Where not reported by the manufacturer, the CDR reviewer calculated differences in proportions and 95% confidence intervals, in additional to pooling of proportion of responders using Review Manager (version 5.0).

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 4: DETAILS OF INCLUDED STUDIES

		STICLO-France	STICLO-Italy
DESIGNS & POPULATIONS	**Study Design**	DB, multi-centre, and phase III RCT	
	Locations	France	Italy
	Randomized (N)	42	23
	Inclusion Criteria	Pre-inclusion criteria for entering one-month baseline period: • Children 3–18 years of age diagnosed with Dravet syndrome, ≥ 4 generalized clonic or tonic-clonic seizures/month receiving concomitant CLO 0.5 mg/kg/day + VPA ≤ 30 mg/kg/day, and with weight ≤ 60 kg Final inclusion criteria for entering DB period: • Children who met the pre-inclusion criteria and participated in the baseline period, ≥ 4 generalized clonic or tonic-clonic seizures/month during the baseline period with normal lab test assessments (CBC, platelets, serum creatinine, and AST and ALT < 3 times the upper limit of normal)	
	Exclusion Criteria	Children receiving other AEDs except for CLO, VPA, progabide, and intrarectal diazepam; asthma patients treated with theophylline; parents could not accurately record the number of seizures; enrolled in another ongoing clinical study	
DRUGS	**Intervention**	Baseline period: • CLO 0.5 mg/kg/day, maximum 20 mg/day • VPA 30 mg/kg/day or less Double-blind period: • STP capsules (250 mg or 500 mg) 50 mg/kg/day as 2 or 3 daily divided doses, PO, in addition to CLO+VPA (at the same doses adopted in baseline)	
	Comparator(s)	Double-blind period: Matching placebo in addition to CLO+VPA	
DURATION	**Phase**		
	Baseline	1 month	
	Double-blind treatment	2 months	
	Follow-up	1 month open-label treatment with STP after DB period	
OUTCOMES	**Primary End Point**	Percentage of responders measured at the end of the double-blind period ("non-responder" was defined as: < 50% reduction in clonic or tonic-clonic seizure frequency during the second month of DB period compared with baseline; withdrawn due to status epilepticus; and other criteria as described in Section 3.2.4)	
	Other End Points	• Percentage of children whose number of clonic or tonic-clonic seizures during the second month of the DB period decreased by ≥ 50% compared with baseline, on a 30-day basis • Change in number of seizures during the DB period (month 1 and month 2) compared with baseline • Percentage of children withdrawn from the study • Time elapsed until the same number of seizures as that in the one-month baseline period were experienced • Safety	
NOTES	**Publications**	Chiron et al.[18]	None

AED = antiepileptic drug; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = cell blood count; CLO = clobazam; DB = double blind; PO = oral; STP = stiripentol; VPA = valproate.
Source: Clinical Study Report for STICLO-France[19] and STICLO[20]; Chiron et al.[18]
Note: Two additional reports were included (CDR submission[3] and Health Canada Reviewer's Report[21]).

3.2 Included Studies

3.2.1 Description of Studies

Two multi-centre, randomized, double-blind, placebo-controlled studies (STICLO-France[19] and STICLO-Italy[20]) met the inclusion criteria for this systematic review (Table 4). The studies compared the efficacy and safety of stiripentol versus placebo as "add-on" therapy to clobazam and valproate in children with Dravet syndrome. Both studies were phase 3 and considered as pivotal studies. The studies included two periods: a one-month baseline period in which all participants received valproate sodium and clobazam, followed by a two-month double-blind period during which eligible patients were randomly assigned to stiripentol or placebo, in addition to valproate and clobazam. After the end of the double-blind period, all patients received stiripentol for 30 days in an open-label manner. The rationale for this one-month stiripentol therapy was not provided.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The two studies had identical patient selection procedures and enrolled patients aged 3 to 18 years. Two stages of recruitment were carried out. Firstly, patients who met all of the following pre-inclusion criteria were allowed into the one-month baseline period:

- a diagnosis of Dravet syndrome according to the diagnostic criteria established by C. Dravet[22]
- at least four generalized clonic or tonic-clonic seizures per month
- receiving clobazam (0.5 mg/kg/day, maximum 20 mg/day) and valproate (30 mg/kg/day or less).

At the end of the baseline period, patients who met all the following final inclusion criteria were allowed into the double-blind period of the study:

- participated in the baseline period
- experienced at least four generalized clonic or tonic-clonic seizures per month during the baseline period while receiving valproate and clobazam therapies
- had a normal laboratory test assessment (cell blood count, platelets, serum creatinine levels and AST and ALT less than 3 times the upper limit of normal).

Patients were ineligible for the double-blind period if: they received antiepileptic medications other than clobazam, valproate, progabide, and intrarectal diazepam; they were asthma patients treated with theophylline; their parents or caregivers could not accurately record the number of seizures; or they were enrolled in another ongoing clinical study.

At the end of the double-blind period, the children involved in the period received open-label stiripentol therapy for 30 days. Evaluations of physical examination, seizure status, and adverse events were performed at the end of this 30-day period.

b) Baseline Characteristics

Baseline characteristics for the two treatment groups were comparable with regard to demographic and disease characteristics, except that the ratio of males to females differed somewhat between the stiripentol and placebo groups in both studies (Table 5). Compared with STICLO-France, patients in the STICLO-Italy study received higher doses of valproate prior to entering the study and during the baseline period. Patients in the STICLO-Italy study also had higher plasma concentration of valproate and reported more tonic-clonic seizures during the baseline period compared with STICLO-France.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	STICLO-France (N = 41)		STICLO-Italy (N = 23)	
	STP N = 21	PL N = 20	STP N = 12	PL N = 11
Age (years)				
Mean (SD)	9.40 (4.00)	9.29 (4.86)	9.17 (3.63)	8.72 (4.43)
Median	NR	NR	NR	NR
Range	3.04–16.67	3.22–20.71[a]	3.72–15.5	3.47–18.9
Gender				
Male, n (%)	6 (28.5)	11 (55.0)	8 (66.7)	5 (45.5)
Female, n (%)	15 (71.4)	9 (45.0)	4 (33.3)	6 (54.5)
Weight (kg)				
Mean (SD	31.8 (12.7)	30.5 (14.4)	31.9 (11.7)	29.2 (9.04)
Median	NR	NR	NR	NR
Range	14.0–60.0	15.0–70.0	16.0–55.0	18.0–49.0
Types of seizures (number of patients experiencing seizures during the baseline period)				
Tonic-clonic seizures Unilateral Bilateral	 4 18	 1 19	 4 10	 5 9
Atypical absence seizures	11	9	3	5
Myoclonus	10	11	13	11
Other	2	4	1	1
Number of tonic-clonic seizures during baseline period				
Mean (SD)	17.9 (17.3)	18.5 (17.0)	33.6 (28.2)	27.4 (28.6)
Range	3.9–72.9	4.1–76.2	2.14–86.1	3.75–101
Doses of AEDs at pre-inclusion, mean (SD)				
CLO (mg/kg)	0.53 (0.25)	0.55 (0.27)	0.58 (0.21)	0.54 (0.18)
VPA (mg/kg)	23.65 (9.47)	24.04 (8.53)	28.2 (7.98)	27.0 (8.42)
Doses of AEDs during baseline period , mean (SD)				
CLO (mg/kg)	0.52 (0.17)	0.48 (0.16)	0.54 (0.14)	0.51 (0.13)
VPA (mg/kg)	21.73 (9.56)	20.70 (8.27)	27.7 (5.75)	25.3 (7.00)
Plasma levels at baseline, median				
CLO, mg/L	0.18	0.17	0.18	0.19
VPA, mg/L	66.7	66.0	85.1	69.6
Nor-CLO, mg/l	0.74	0.81	0.63	0.45

AED = antiepileptic drug; CLO = clobazam; nor-CLO = norclobazam; NR = not reported; PL = placebo; SD = standard deviation; STP = stiripentol; VPA = valproate.

[a] One patient in the placebo group was 20.7 years old.

Source: Clinical Study Reports for STICLO-France[19] and STICLO-Italy.[20]

3.2.3 Interventions

During the baseline period, patients in both studies received clobazam 0.5 mg/kg/day (maximum 20 mg/day). The dose of valproate had to be decreased to lower than 30 mg/kg/day if they were receiving high doses (30 to 40 mg/kg/day) prior to entering the baseline period.

During the two-month double-blind period, patients who were randomized to stiripentol therapy received the drug orally at a dose of 50 mg/kg/day (divided into two or three doses). Stiripentol was administered as capsules that were not supposed to be opened. If it was necessary to open a capsule, it was recommended that the contents be mixed with sugared food. It is unclear whether the placebo group was matched in the same way.

During the double-blind period, doses of concomitant valproate and clobazam were reduced in the case of serious adverse events; the dose of valproate could be decreased by 10 mg/kg/day in case of poor appetite or persistent weight loss (this was not defined in the studies), and clobazam could be decreased by 25% in case of drowsiness or hyperexcitability. If these events persisted during the two weeks following the decrease of the dose, patients were to be withdrawn from the study.[18-20]

In STICLO-France, treatment compliance was evaluated by calculating the ratio between the number of missing capsules in the bottles and the number of prescribed capsules in both treatment groups. The number of capsules left at the end of each visit and the end of the treatment were counted. In STICLO-Italy, compliance was evaluated by counting the number of capsules left at the end of the treatment. Plasma concentrations of stiripentol were measured at the end of the double-blind period in both studies to assist in examining treatment compliance. Plasma concentrations of co-administered drugs (valproate and clobazam) were also measured to assess the potential interactions between stiripentol and these drugs.

Progabide or intrarectal diazepam was allowed in all study periods in cases of long and severe seizures (no descriptions of "long and severe" appeared in the two studies). In STICLO-France, 7 patients (5 in the stiripentol group and 2 in the placebo group) received progabide, and 5 patients (3 in the stiripentol group and 2 in the placebo group) received diazepam before entering the baseline period. In STICLO-Italy, no patients received progabide prior to entering the study, while diazepam was occasionally provided to the patients throughout the study in case of seizure or agitation. Information regarding the doses and frequency of these two drugs was not reported.

3.2.4 Outcomes

a) Primary Outcome in Both Studies

The percentage of responders (children who did not fall into any of the non-responder categories) was measured at the end of the double-blind period.

Definition of "Non-responder"

- After two months of treatment, the number of generalized clonic or tonic-clonic seizures experienced during the second month of the double-blind period had not decreased by at least 50% compared with the number of seizures during the baseline period
- Patients who were withdrawn from the study because of the occurrence of status epilepticus
- Patients whose number of seizures had increased by more than 50%, compared with the baseline period, within 0 to 20 days after entry into the double-blind period
- Patients who, during the baseline period, had an increase of more than 50% in the number of seizures (compared with the period before baseline) and whose seizures, during the first month of the double-blind period, did not return to the previous number before the baseline period.

b) Secondary Outcomes

Secondary outcomes included:

- The percentage of children whose number of generalized clonic or tonic-clonic seizures during the second month of the double-blind period decreased by at least 50% compared with that during the baseline period
- The mean number of seizures during the double-blind period (month 1 and month 2 were considered separately) in comparison with the number of seizures during the baseline in each group.

The number of seizures was recorded by the parents in a diary on a daily basis. The types and number of seizures were recorded in the case report form by the investigators at each patient visit during the double-blind period. Only generalized clonic or tonic-clonic seizures were assessed in efficacy analyses because these are the most disabling types of seizure; they are also more common and easier to identify than other types of seizures, such as absence seizures. Therefore, all seizure-relevant outcomes in this report refer to "generalized clonic or tonic-clonic seizures."

c) Safety

The frequency and severity of adverse events were recorded by the investigators for each treatment group on the case report form.

3.2.5 Statistical Analysis

Categorical variables (e.g., percentage of responders and number of patients with an adverse event) were compared using a chi-squared test, and continuous variables (e.g., number of seizures and plasma concentrations of antiepileptic drugs) were compared using the non-parametric Mann-Whitney test. Both studies indicated that intention-to-treat (ITT) analyses were performed for efficacy. The ITT population was defined as all randomized patients who received at least one dose of the study treatment with at least one end point assessed, and the per-protocol (PP) population was defined as all patients who duly completed the study with no major deviation from the protocol.[23]

A sample size calculation was not performed a priori in either STICLO-France or STICLO-Italy. In STICLO-France, a preliminary analysis was planned after 40 patients were enrolled (with 20 in each treatment group), with the intention to stop the study if a clinically relevant difference was demonstrated. The difference considered to be clinically relevant was decided at the time of the analysis. Specifically, if the lower bound of the 95% confidence interval (CI) for the between-treatment difference in the percentage of responders was greater than 25%, the study would be stopped. The 25% difference was chosen according to previous clinical trials of epileptic disorders. The investigators indicated that, based on 40 patients, the study would have sufficient power to detect a difference (between stiripentol and placebo) of 25% in the percentage of responders, without specifying the level of power.[18] STICLO-Italy was a supplement to STICLO-France, and it was planned to include 20 patients. The rationale for recruiting 20 patients was not described.

Both studies indicated that adjustment of the covariates was not necessary when assessing the efficacy of stiripentol, due to the comparability between the treatment groups. Imputation was not attempted in replacing missing data for any outcome measures. The STICLO-France study stated that analyses were performed based on available data. Multiple comparison adjustments were not performed in either study to correct the type 1 error rate.

a) Analysis Populations

The manufacturer indicated that the comparisons between the two treatment groups were carried out in the ITT population (see previous section for the definitions of ITT and PP populations). One patient in the stiripentol group in STICLO-France had a major protocol violation (treatment was taken irregularly and the number of seizures was not recorded in the diary, causing missing efficacy data). This patient was excluded from efficacy analysis.

In the two studies, the safety analysis took into account all enrolled patients; however, in the STICLO-France study, the aforementioned patient who was excluded from the efficacy analysis did not present with an adverse event, and the patient was not counted in the total number of patients evaluated for safety during the double-blind period.

3.3 Patient Disposition

Patient disposition for each included study is presented in Table 6. The number of patients randomized was 42 and 23 in the STICLO-France and STICLO-Italy studies, respectively. More patients in the placebo groups dropped out compared with the stiripentol groups in both STICLO-France and STICLO-Italy (20% versus 5%, and 18% versus 8% respectively).

In STICLO-France, five patients did not enter the baseline period for the following reasons (one patient per reason): status epilepticus, did not tolerate clobazam, fewer than four seizures per month plus neutropenia, did not have Dravet syndrome, and study terminated before enrolment. During the double-blind period, one patient in the stiripentol group was not evaluable; therefore, that patient was excluded from efficacy and safety analysis. In STICLO-Italy, one patient included in the baseline period did not enter the double-blind period, but the reason for this exclusion was not provided in the clinical study report.

No patient was lost to follow-up in either study.

TABLE 6: PATIENT DISPOSITION

	STICLO-France		STICLO-Italy	
	STP	PL	STP	PL
Screened, N	47		24	
Randomized, N	22	20	12	11
Discontinued study, N (%)	1 (5)	4 (20)	1 (8)	2 (18)
Adverse events	1	2	1	0
No improvement		2		1
Worsening				1
Status epilepticus	1	1		
Drowsiness, motor deficiency		1		
ITT, N (%)	22 (100)	20 (100)	12 (100)	11 (100)
PP, N (%)	21 (95.5)[a]	20	11 (91.7)	9 (81.8)
Safety, N (%)	21 (95.5)[a]	20 (100)	12 (100)	11 (100)

ITT = intention to treat; NR = not reported; PL = placebo; PP = per protocol; STP = stiripentol.
[a]One patient in the STP group had a major protocol violation and was excluded from the efficacy and safety analysis (treatment was taken irregularly and the number of seizures was not recorded in the diary).
Source: Clinical Study Reports for STICLO-France[19] and STICLO-Italy;[20] manufacturer's response to CDR's request for additional information.[23,24]

3.4 Exposure to Study Treatments

In STICLO-France, treatment adherence to the study drug was evaluated for 22 out of 41 patients. Nineteen patients did not return all the bottles: 11 in the stiripentol group and 8 in the placebo group. Treatment adherence ranged from 57% to 164%, with a median value of 100%. The mean (SD) treatment duration was 57.3 (SD 5.9) days in the stiripentol group and 50.3 (SD 17.2) days in the placebo group.

In STICLO-Italy, the bottles were not required to be returned at the end of the treatment; serum concentrations of stiripentol were measured to provide evidence of treatment adherence.

3.4.1 Doses and Plasma Concentration of Antiepileptic Drugs

Doses and plasma concentrations of stiripentol and co-administered antiepileptic drugs are presented in Table 7.

a) Stiripentol

The mean dosage of stiripentol was 48.9 (SD 2) mg/kg/day during the double-blind period in STICLO-France, and it was 50.6 (SD 4.2) mg/kg/day in STICLO-Italy. In both studies, the doses of stiripentol were consistent with Health Canada–recommended dosages. Plasma concentrations of stiripentol at the end of the double-blind period were measured to assist in assessing treatment adherence.

b) Co-administered Antiepileptic Drugs

Doses of the co-administered antiepileptic drugs in the double-blind period were allowed to be decreased due to adverse events. In STICLO-France, 11 (52.4%) patients in the stiripentol group and 3 (15%) patients in the placebo group had to reduce their doses of clobazam or valproate. The number of patients who needed to reduce the doses of concomitant medications was not reported in STICLO-Italy.

Treatment exposure to the concomitant antiepileptic drugs was examined by measuring the plasma concentrations of clobazam, valproate, and norclobazam at the end of the baseline period, as well as the end of the double-blind period.

At the end of the double-blind period, the steady-state plasma concentrations of clobazam and its metabolite, norclobazam, increased from baseline in the stiripentol groups. Compared with clobazam, the increase in norclobazam was of a greater magnitude: from a median of 0.74 mg/L to 4.14 mg/L in STICLO-France, and from a median of 0.63 mg/L to 4.01 mg/L in STICLO-Italy. In contrast, in the placebo groups, there was little change in the plasma concentrations of either clobazam or norclobazam from baseline to the double-blind period. The changes in plasma concentration of valproate were inconsistent between STICLO-France (decreased from baseline) and STICLO-Italy (increased from baseline).

TABLE 7: DOSES AND PLASMA CONCENTRATION OF ANTIEPILEPTIC DRUGS DURING BASELINE AND DOUBLE-BLIND PERIODS

	STICLO-France		STICLO-Italy	
	Stiripentol (N = 22)	Placebo (N = 20)	Stiripentol (N = 12)	Placebo (N = 11)
Doses of antiepileptic drugs				
Stiripentol, mg/kg/d				
DB	Mean 48.9 (2)	–	Mean 50.6 (4.2)	–
Clobazam, mg/kg/d				
Baseline	Mean 0.52 (0.17)	Mean 0.48 (0.16)	Median 0.50	Median 0.50
DB	NR	NR	NR	NR
Valproate, mg/kg/d				
Baseline	Mean 21.73 (9.56)	Mean 20.70 (8.27)	Median 27.7 (5.75)	Median 25.3 (7.00)
DB	NR	NR	NR	NR
Plasma levels of antiepileptic drugs				
Stiripentol, mg/L				
DB	Mean 10 (3.6)	–	Mean 10.2 (2.98)	–
Clobazam, mg/L				
Baseline	Median 0.179	Media 0.170	Median 0.177	Median 0.189
DB	Median 0.244 *P* < 0.01 vs. PL	Median 0.198	Median 0.225 *P* NS vs. PL	Median 0.201
Norclobazam, mg/L				
Baseline	Median 0.74	Median 0.81	Median 0.625	Median 0.450
DB	Median 4.14 *P* < 0.001 vs. PL	Median 0.80	Median 4.01 *P* < 0.002 vs. PL	Median 0.49
Valproate, mg/L				
Baseline	Median 66.7	Media 66.0	Median 85.1	Median 69.6
DB	Median 66.5 *P* NS vs. PL	Median 58.7	Median 87.7 *P* NS vs. PL	Median 78.1

DB = double blind; NR = not reported; NS = non-significant; *P* = *P* value; PL = placebo; vs = versus.

3.5 Critical Appraisal

3.5.1 Internal Validity

STICLO-France and STICLO-Italy were randomized, double-blind, multi-centre trials. Allocation of treatments was performed using a computer-generated randomization list. The active drug and the placebo were strictly identical in appearance. Within studies, patient clinical and demographic characteristics were generally balanced, except for gender.

The quality of the included studies was potentially compromised due to the following concerns:

- The frequency of study discontinuation was higher in the placebo groups compared with the stiripentol groups in both studies. However, since it is unclear how missing data were handled, it is unclear to what extent this differential dropout affects study results.

- According to the clinical expert, the dose of co-administered clobazam was on the lower end of what would be used in clinical practice (a maximum dose of 20 mg/day adopted in the two studies versus 40 mg/day recommended by Health Canada for children aged 2 to 16 years). When stiripentol is added to the existing antiepileptic therapy (clobazam in this case), it increases the plasma concentration of that drug and its metabolite; however, in the placebo group, patients receiving a relatively low dose of clobazam may be expected to have a suboptimal treatment response, thus overestimating the benefit of stiripentol.
- Power calculations were not performed in either study. Rather, investigators inappropriately determined a between-treatment difference for the primary outcome for statistical testing after the study was under way.
- Parent or caregiver reporting of the number of seizures: Parents and caregivers recorded patients' seizure frequency in a diary; however, this method has not been validated and the reliability of this method is questionable; also it was not clear if, prior to the patient enrolment in the study, parents and caregivers received training on how to recognize and accurately report seizures. Patient and caregiver adherence to daily reporting of seizure frequency was not reported.
- Insufficient data reporting: There were no definitions of the analyzed populations, which created confusion in determining the ITT and PP population. As well, given the small study population and potential for skewed (non-normal) data distributions, medians of continuous variables were preferable as a measure of central tendency, yet these were rarely reported. On the other hand, a non-parametric test was appropriately employed for the comparison of continuous outcomes in non-normally distributed data.
- Even though both studies indicated that ITT analysis was performed for efficacy, only PP data were reported for some outcomes, such as the change from baseline in number of seizures during the second month of the double-blind period in STICLO-Italy. The results for this outcome were measured based on 36 patients in STICLO-France, and 20 patients in STICLO-Italy. In STICLO-France, although the study indicated that ITT analyses were performed, it also stated the analyses were performed on available data only. Therefore, data analyses were not performed in true ITT population in the two studies.
- In STICLO-France, it is difficult to assess adherence when the medication count was conducted for only one-half (approximately) of the study population (19 patients failed to return the bottles). In STICLO-Italy, the bottles were not returned to investigators so adherence could not be verified by medication count, and only plasma concentrations of stiripentol and co-administered antiepileptic drugs were measured at the end of the study; therefore, it is unclear if the patients were adherent throughout the study. In addition, the blood test could not provide information on treatment adherence for placebo.

3.5.2 External Validity

According to the clinical expert consulted for this review, the baseline patient characteristics in the two studies are reflective of the typical Canadian population seen in clinical practice, even though the studies were conducted in Europe more than 15 years ago. The diagnostic criteria developed by Charlotte Dravet in the 1980s are still valid in patient selection. The only difference might be the current availability of genetic testing for *SCN1A* to assist with a diagnosis of Dravet syndrome. Patients aged 3 to 18 years were enrolled in the studies, therefore, the efficacy and safety of stiripentol in patients out of this age range is uncertain.

The dose of stiripentol employed in the two studies is consistent with the Health Canada–recommended dose, and with the dose used by the clinical expert in practice. Comparators adopted in the two studies were appropriate, however, the dose of clobazam was relatively low as described previously.

Outcome measures assessed in the studies are clinically relevant; however, some important clinical outcomes were not assessed, such as health-related quality of life, frequency of status epilepticus, and health care utilization.

Long-term use of antiepileptic drugs is expected in clinical settings when patients respond well to the treatment, and the adverse effects of the treatment are tolerable. Both STICLO-France and STICLO-Italy were short-term studies with a treatment duration of two months; hence, the included studies do not provide evidence of long-term efficacy and harm of stiripentol in patients with Dravet syndrome. In addition, small sample sizes preclude the identification of infrequent or rare adverse events.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Section 2.2, Table 3) are reported here. Results for key efficacy outcomes are presented in Table 8. In all the studies, stiripentol was compared with placebo. Note that, in this report, all seizure outcomes refer to generalized clonic or tonic-clonic seizures.

3.6.1 Seizure-Free Status

Nine (45%) and three (27%) stiripentol-treated patients in STICLO-France and STICLO-Italy, respectively, reported no seizures during the second month of the double-blind period, while in the placebo groups, all patients still experienced at least one episode of clonic or tonic-clonic seizures. *P* values were not reported for the comparisons between stiripentol and placebo.

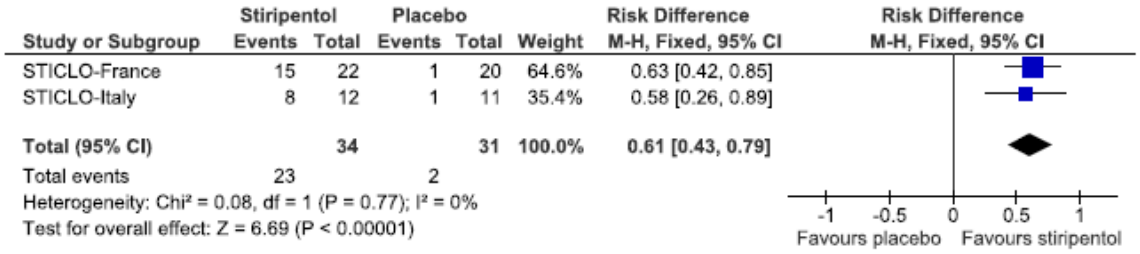
3.6.2 Percentage of Responders and Percentage Achieving a Greater Than 50% Reduction in Clonic or Tonic-Clonic Seizures

In STICLO-France, the percentage of responders was statistically significantly higher in the stiripentol group compared with placebo: 71.4% versus 5.0%; between-treatment difference (95% CI), 66.4% (42.2% to 85.7%). No results from PP population were reported. In STICLO-France, the percentage of children with at least a 50% decrease in seizures during the second month of the double-blind period was statistically higher in the stiripentol group compared with placebo: 71.4% versus 5.0%, respectively ($P < 0.00002$). This percentage was identical to the frequency of responders and concerned the same children.

In STICLO-Italy, the percentage of responders was statistically significantly higher in the stiripentol group compared with placebo in the ITT population: 66.7% versus 9.1%, between-treatment difference (95% CI), 57.6 (NR). Results from the PP analysis were similar to the ITT population: 72.7% vs. 11.1%, $P = 0.01$. The percentage of children with at least 50% decrease in seizure frequency at the end of the second month of double-blind period compared with baseline was 66.7% in the stiripentol group versus 9.1% in the placebo group (*P* value was not reported).

Data pooling conducted by CDR that included all randomized patients confirmed that the proportion of responders was statistically significantly higher in stiripentol-treated patients versus placebo (RD [95% CI], 0.61 [0.43 to 0.79]), $P < 0.00001$). Heterogeneity was not detected.

Figure 2. Proportion of Responders Between Stiripentol and Placebo (STICLO-France and STICLO-Italy)



3.6.3 Seizure Frequency

In STICLO-France, the change in the number of seizures from baseline was greater in the stiripentol group compared with the placebo group during the first month of the double-blind period; the number of seizures decreased from 17.9 to 2.7 in the stiripentol group, but increased from 18.5 to 23.8 in the placebo group ($P < 0.001$ for the between-group comparison).

In STICLO-Italy, the change in the number of seizures from baseline was also greater in the stiripentol group compared with the placebo group during the first month of the double-blind period; the number of seizures decreased from 33.6 to 4.7 in the stiripentol group, but increased from 27.4 to 29.0 in the placebo group ($P < 0.05$ for the between-group comparison).

Compared with baseline, the number of seizures during the second month of the double-blind period decreased in both the stiripentol and placebo groups; however, more reductions were observed in the stiripentol groups. The between-group difference did not reach statistical significance in the STICLO-Italy (Table 8). Note that during the second month for both studies, this outcome was calculated based on patients who had completed the study.

3.6.4 Other Efficacy Outcomes

a) Reduction in Episodes of Status Epilepticus

This outcome was not reported in the efficacy analysis. However, while frequency of status epilepticus was not an efficacy outcome of the trials, it was included in the harms data (Table 9).

b) HRQoL

This outcome was not measured in the included studies.

c) Death (All-Cause and Sudden Unexplained Death in Epilepsy)

No deaths were reported during the study.

d) Health Care Utilization

This outcome was not measured in the included studies.

TABLE 8: KEY EFFICACY OUTCOMES

	STICLO-France		STICLO-Italy	
	STP (N = 22)	PL (N = 20)	STP (N = 12)	PL (N = 11)
Seizure-free status during the second month of DB period				
n/N (%)	9/20 (45)	0/16	3/11 (27)	0/9
P value (STP vs. PL)	NR		NR	
Proportion of responders				
n/N (%)	15/21 (71.4)	1/20 (5.0)	8/12 (66.7)	1/11 (9.1)
Between-group difference and 95% CI, STP vs. PL (%)	66.4[a] (42.2 to 85.7)		57.6[a] (NR)	
P value (STP vs. PL)	< 0.00002		0.009	
Percentage of children with ≥ 50% decrease in seizures during the second month of DB period				
n/N (%)	15/21 (71.4)	1/20 (5.0)	8/11 (73)	1/9 (11)
P value (STP vs. PL)	< 0.00002		NR	
Number of tonic-clonic seizures in the first month vs. baseline, mean (SD)				
Baseline	17.9 (17.3)	18.5 (17.0)	33.6 (28.2)	27.4 (28.6)
The first month	2.72 (4.06) (n = 21)	23.82 (36.55) (n = 20)	4.7 (7.3) (n = 12)	29.0 (35.6) (n = 11)
P value (STP vs. PL)[b]	< 0.001		< 0.05	
Number of tonic-clonic seizures in the second month vs. baseline[c], mean (SD)				
Baseline	17.9 (17.3)	18.5 (17.0)	33.6 (28.2)	27.4 (28.6)
The second month	5.15 (7.73) (n = 20)	13.80 (7.33) (n = 16)	9.8 (10.0) (n = 11[d])	16.7 (11.3) (n = 9[d])
P value (STP vs. PL)[b]	< 0.002	–	NS	–
Death				
n (%)	0	0	0	0

CI = confidence interval; DB = double blind; NR = not reported; NS = non-significant; PL = placebo; SD = standard deviation; STP = stiripentol, vs = versus.

[a] Calculated by CDR.

[b] The *P* value was reported in the manufacturer analysis using Mann-Whitney test.

[c] The mean number of seizures and related variation during the second month of the double-blind period compared to baseline were calculated in patients who had completed the study.

[d] Per-protocol population data.

Source: Clinical Study Reports for STICLO-France[19] and STICLO-Italy.[20]

3.7 Harms

Only those harms identified in the review protocol are reported in this section.

3.7.1 Adverse Events

In the two studies, the percentage of patients reporting adverse events was higher in the stiripentol group compared with the placebo group (Table 9). Adverse events were reported as being mild or moderate in severity. In STICLO-France, the most commonly reported adverse events with stiripentol included drowsiness, appetite loss, and weight loss. In the placebo group, the most commonly reported adverse events were drowsiness and weight gain.

In STICLO-Italy, the most commonly reported adverse events in the stiripentol group were sleepiness, behaviour disorders, and loss of appetite. In the placebo groups, sleepiness, ataxia, hyperexcitability, irritability, tremors, hyperkinesia, and loss of appetite were reported.

3.7.2 Serious Adverse Events

In STICLO-France, six patients (28.6%) in the stiripentol group and three patients (15%) in the placebo group reported serious adverse events.

In STICLO-Italy, no serious adverse events were reported during the study.

3.7.3 Withdrawal Due to Adverse Events

In STICLO-France, one patient in the stiripentol group withdrew due to an adverse event (status epilepticus) compared with four patients in the placebo group (status epilepticus, major drowsiness, and repeated seizures) (Table 9).

In STICLO-Italy, one patient in the stiripentol group withdrew due to symptoms of drowsiness. No patients in the placebo group withdrew from the study due to adverse events.

3.7.4 Mortality

No deaths occurred during the study.

3.7.5 Notable Harms

a) Neutropenia, AST, and ALT

Both the STICLO-France and STICLO-Italy reports indicated that no clinically significant individual laboratory test abnormality was observed for levels of neutrophils, AST, and ALT.

TABLE 9: HARMS

	STICLO-France		STICLO-Italy	
	STP (n = 21)	PL (n = 20)	STP (n = 12)	PL (n = 11)
AEs				
Patients with > 0 AEs, N (%)	21 (100)	9 (45)	10 (83)	3 (27)
Most common AEs[a]:				
Drowsiness	15 (71)	2 (10)	NR	NR
Sleepiness	NR	NR	7 (58.3)	1 (9.1)
Hyperexcitability/agitation	5 (24)	0	2 (16.7)	1 (9.1)
Aggressiveness	3 (14)	0	2 (16.7)	1 (9.1)
Hypotonia	2 (9.5)	1 (5)	3 (25)	0
Ataxia	3 (14)	1 (5)	1 (8.3)	2 (18.2)
Tremors	3 (14)	0	0	1 (9.1)
Appetite loss	7 (33)	1 (5)	6 (50)	1 (9.1)
Nausea/vomiting	2 (9.5)	1 (5)	3 (25)	0
Weight loss	6 (28.5)	0	2 (16.7)	0
Weight gain	5 (24)	4 (20)	NR	NR
Neutropenia (< 1.50 and > 1.00 $10^9.1^{-1}$)	3 (14)	0	NR	NR
SAEs				
Patients with > 0 SAEs, N (%)	6 (28.6)	3 (15)	0	0
Most common SAEs	SE, severe drowsiness/ hypotonia, weight loss, giant urticaria; aggressiveness, abdominal pain	Severe drowsiness, absence SE, repeated seizures	No SAE	

	STICLO-France		STICLO-Italy	
	STP (n = 21)	PL (n = 20)	STP (n = 12)	PL (n = 11)
WDAEs				
WDAEs, N (%)	1 (4.8)	2 (10)	1 (8.3)	0
Most common reasons	SE	Severe drowsiness, absence seizures, repeated seizures	Drowsiness and balance symptoms	

AE = adverse event; PL = placebo; SAE = serious adverse event; SE = status epilepticus; STP = stiripentol; WDAE = withdrawal due to adverse event.

[a] Frequency > 10%.

Source: Clinical Study Reports for STICLO-France[19] and STICLO-Italy.[20]

4. DISCUSSION

4.1 Summary of Available Evidence

Two multi-centre, randomized, parallel-group, double-blind, placebo-controlled studies, STICLO-France (N = 42) and STICLO-Italy (N = 23), met the inclusion criteria for this systematic review. The two studies employed similar study designs to compare the efficacy and safety of stiripentol with placebo in patients 3 to 18 years old, with a diagnosis of Dravet syndrome, who were being treated concomitantly with clobazam and valproate. Both were phase 3 and considered pivotal studies. They both included a one-month baseline period in which patients received stable doses of clobazam and valproate, and a two-month double-blind period (when stiripentol was administered orally at a dose of 50 mg/kg/day in combination with clobazam and valproate), followed by a one-month period of open-label stiripentol therapy for all study participants. The primary outcome measure was the proportion of responders during the double-blind period.

4.2 Interpretation of Results

4.2.1 Efficacy

The effect of stiripentol on seizure control was measured using various measures: proportion of patients achieving seizure-free status at study end point, proportion of responders (primary outcome measure), percentage of patients with a greater than 50% reduction in the number of seizures from baseline, and change from baseline in the mean number of seizures. Results for all the above outcomes consistently favoured stiripentol over placebo. After two months of double-blind treatment, the percentage of responders was statistically significantly greater in the stiripentol groups compared with placebo in both studies, and the percentage of patients achieving a greater than 50% reduction in seizures was statistically significantly greater in the stiripentol group in STICLO-France (statistical significance not reported in STICLO-Italy). The reduction in the number of seizure episodes compared with baseline, over both the first and second months of the double-blind period, were greater in stiripentol groups compared with placebo in both studies, but did not reached statistical significance in the second month of the STICLO-Italy study. A higher percentage of patients in the stiripentol groups were reported to be seizure free compared with placebo: 27% and 45% in the stiripentol groups compared with 0% in the placebo groups. There are a number of concerns with the available evidence, including uncertainties regarding handling of missing data. For example, the denominator used in the reporting of seizure-free status excluded some patients, but the reason for this was unclear. There were no data on frequency of status epilepticus, health-related quality of life, or health care utilization. Neither study reported efficacy results for the subgroups included in the CDR protocol: age, seizure type, and *SCN1A* mutation status.

However, it is recognized that Dravet syndrome is a rare condition, thus it can be impractical to attain sample sizes which would enable subgroup analyses.

Stiripentol inhibits several cytochrome P450 isoenzymes, leading to pharmacokinetic interactions with numerous drugs, including co-administered antiepileptics. The stiripentol product monograph recommends monitoring of plasma levels of anticonvulsants concomitantly administered with stiripentol, with possible dosage adjustments of the concomitantly administered antiepileptics. In the included studies, plasma levels of norclobazam (an active metabolite of clobazam) were noticeably elevated over baseline levels in the stiripentol groups (from 0.74 mg/L to 4.14 mg/L in STICLO-France, and from 0.625 mg/L to 4.01 mg/L in STICLO-Italy), with no corresponding increase in the placebo groups, suggesting that the antiepileptic activity of stiripentol may be mediated through its effect on concomitantly administered clobazam. In addition, the clinical expert consulted for this review indicated that the dose of clobazam used in the studies was lower than that used in clinical practice; thus, patients in the placebo groups may have been inadequately treated, leading to an overestimation of the benefit to be achieved with the addition of stiripentol. The lower dose of clobazam was considered acceptable by the Health Canada reviewer because the manufacturer asserted that the dose adjustment was done for safety and tolerability reasons and represented the real-life use of clobazam in conjunction with stiripentol; in addition, analysis of individual patient data by Health Canada showed that during the baseline period, the dose of clobazam was slightly decreased from the pre-enrolment period; yet the reduction in the dose of clobazam did not result in increased seizure frequency during the baseline period, which could have exaggerated the effect of stiripentol during the double-blind period.[21] Despite the acceptance by the Health Canada reviewer of the manufacturer's rationale for the use of a lower clobazam dose, it should be noted that the rationale applies to stiripentol-treated patients; the dose of clobazam in the placebo group may still be suboptimal and patients in the placebo group may not be representative of how patients are treated in clinical practice. In addition, examination of individual patient data by Health Canada was based on a small number of patients; therefore, the impact of change in clobazam dosage on seizure control was not conclusive.

In both STICLO-France and STICLO-Italy, the seizure frequency was recorded by patients' parents or caregivers in a diary; however, in this particular population, accurate identification, differential diagnosis and reliable recording of seizure frequency can be very challenging. In a retrospective study examining the accuracy of caregiver report of seizures in children with epilepsy, the sensitivity of seizure identification (any type) by parents was only 43.1%. The poor performance was due mainly to the lack of awareness of the subtle clinical features of some seizures and the lack of witnesses at the time the seizure occurred. The types of seizures also play a role in the accuracy of the recording: tonic, tonic-clonic, and atonic seizures were less likely to be missed, while absence seizures and nocturnal seizures had a higher chance of being missed.[25] On the other hand, the patients, especially younger patients, are often unable, due to intellectual or communication difficulties, to describe their symptoms, so clinicians have to rely on caregivers' observations and reports.[26] While it may be difficult to accurately count seizures, and the need for "proxy reporting" by parents or caregivers adds uncertainty to the validity of the information reported, these studies focused on generalized clonic or tonic-clonic seizures, which are most easily identified, mitigating the issue of relying on parent or caregiver reporting. In addition, accuracy in reporting is not expected to differ based on treatment.

The included studies do not provide evidence of long-term efficacy. This is of concern given that treatment for Dravet syndrome will be required for many years and neither of the trials included adult patients. One single-group open-label trial of stiripentol with a limited number of adult patients was identified. This trial reported reduction in seizure frequency over 52 weeks compared with baseline (see APPENDIX 4: ADDITIONAL EFFICACY AND SAFETY EVIDENCE FOR STIRIPENTOL IN THE TREATMENT OF DRAVET SYNDROME). However, these findings should be interpreted with caution given the lack of a comparator group. The included studies did not address other non-seizure–related consequences of Dravet syndrome. Dravet syndrome is associated with poor psychomotor development and high mortality, often due to status epilepticus and its consequences; however, none of those outcomes were assessed in the included studies. Finally, the study did not compare stiripentol to other antiepileptic drugs that may be added on to clobazam and valproate. CDR identified several clinical trials examining the use of both levetiracetam and topiramate as add-on treatment to clobazam and valproate in the treatment of Dravet syndrome (See APPENDIX 5: EFFICACY AND SAFETY EVIDENCE FOR LEVETIRACETAM AND TOPIRAMATE IN THE TREATMENT OF DRAVET SYNDROME). The trials were considered to be low-quality evidence (open-label single-group trials); however, according to the clinical expert consulted for this review, these drugs are used to treat Dravet syndrome despite their lack of an explicit Health Canada indication for this condition.

4.2.2 Harms

In both included studies, adverse events were higher in the stiripentol groups compared with the placebo groups, and were reported as being mild or moderate in severity. The most frequently reported adverse events were drowsiness and behavioural, gastrointestinal, and neurological disorders. Loss of appetite and corresponding weight loss were an important consideration for the pediatric patients. Both studies reported a higher percentage of patients with appetite loss and weight loss in the stiripentol groups than in the placebo groups. In the STICLO-Italy study, safety data regarding serious adverse events were not explicitly reported. In STICLO-France, patients in the stiripentol group reported more serious adverse events.

As noted previously, stiripentol inhibits several cytochrome P450 isoenzymes, creating a high risk of interactions, including with co-administered antiepileptic drugs. Previous studies suggested that some adverse events associated with stiripentol were related to the elevated plasma concentration of valproate and clobazam after the addition of stiripentol, and that these adverse events disappeared when the dose of the co-administered drug was decreased.[12,27] Other studies indicated that co-administration with stiripentol increased the concentration of both clobazam and norclobazam; however, the increase in norclobazam levels was more pronounced compared with the increase in clobazam levels.[28] Such changes were observed in the two STICLO studies, at least for norclobazam, and this could be expected to be associated with a higher frequency of adverse events known to be associated with clobazam. In STICLO-France and STICLO-Italy, doses of valproate and clobazam were to be decreased in cases of serious adverse events. In STICLO-France, compared with placebo, more patients in the stiripentol group required dose reductions (stiripentol: 11 patients reduced dose of clobazam, and 6 reduced dose of valproate; placebo: 3 patients reduced dose of clobazam and no patient reduced dose of valproate). In STICLO-Italy, in the stiripentol group, 4 patients reduced dose of clobazam and 2 reduced dose of valproate, while no patient needed to reduce doses of clobazam or valproate in the placebo group.[24] Since stiripentol was administered in conjunction with clobazam and valproate, it is not possible to discern adverse events that may be specifically attributed to stiripentol.

Finally, given the short duration of the studies, there is limited evidence of long-term safety, and the small sample sizes preclude the identification of infrequent or rare adverse events. In one uncontrolled open-label study investigating benefits and harms of stiripentol added on to clobazam and valproate for 52 weeks, there were no deaths or withdrawal due to adverse events over 52 weeks. The safety profile of adjunctive stiripentol therapy in the 52-week study was similar to what was observed in the two short-term studies. For more detailed information, see APPENDIX 4: ADDITIONAL EFFICACY AND SAFETY EVIDENCE FOR STIRIPENTOL IN THE TREATMENT OF DRAVET SYNDROME.

5. CONCLUSIONS

Based on a systematic review of two double-blind RCTs, compared with placebo, adjunctive therapy with stiripentol 50 mg/kg/day (added on to clobazam and valproate) resulted in statistically significantly reduced seizure frequency and a higher percentage of responders among pediatric patients with Dravet syndrome over two months. However, the combination of the relatively low dose of clobazam used, and the pharmacokinetic drug–drug interaction that resulted in elevated levels of norclobazam in the stiripentol groups but not the placebo groups, may have overestimated the benefit of stiripentol.

Adverse events and serious adverse events occurred more frequently in stiripentol-treated patients compared with placebo. Drowsiness, sleepiness, appetite loss, weight loss, and hyperexcitability were the most common complaints from patients receiving stiripentol. The elevated levels of norclobazam in the stiripentol-treated patients may have contributed to the higher frequency of adverse events. Since stiripentol was administered in conjunction with clobazam and valproate, it is not possible to discern adverse events that may be specifically attributed to stiripentol.

Finally, given the short duration of the studies, there is limited evidence of long-term efficacy and safety and there is a lack of data on other outcomes of interest such as health-related quality of life and health care utilization.

APPENDIX 1: PATIENT INPUT INFORMATION

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input

Dravet.ca is the Canadian network for families, friends, and caregivers of people with Dravet spectrum disorders. The organization serves to educate families and the public about Dravet spectrum disorders by providing conferences, family retreats, and lectures to the medical community, and collecting and disseminating information on this topic. Dravet.ca is a charitable organization and undertakes activities ancillary and incidental to the attainment of charitable purposes. Dravet.ca is governed by a board of directors comprised of eight members. The following conflict of interest was declared: Biocodex Laboratories was a sponsor of the 2012 Dravet.ca Family, Physician, and Researcher Conference and the sponsorship provided was $10,000. No conflicts were declared regarding compilation of this submission.

2. Condition and Current Therapy-Related Information

Dravet syndrome is a catastrophic form of epilepsy that typically begins during the first year of life. Seizures are severe and difficult to control. Children experience frequent seizures, multiple seizure types, prolonged seizures, and episodes of life-threatening status epilepticus.

In November 2013, Dravet.ca conducted an online survey of caregivers with a child with Dravet syndrome. The majority of children (50%) cared for by caregivers were between 10 and 17 years of age. Responses were received from 19 caregivers (16 Canadians and 3 non-Canadians); however, only responses from Canadian caregivers were analyzed for this submission.

All survey respondents reported that their family member with Dravet syndrome had experienced tonic-clonic (grand mal) seizures. The lowest frequency reported for tonic-clonic seizures (n = 16) ranged from less than 1 per month to 13 to 20 per month (mode = less 1 per month). The highest frequency (n = 16) ranged from 1 to 4 per month to 350 per month (mode = more than 50 per month). The other seizure types reported were: myoclonic (88%); hemi-clonic (75%); absence (88%); atypical absence (69%); clonic (56%); tonic (69%); atonic (81%); partial or focal seizures (69%); and other seizures (25%). All respondents reported that their child, or the person in their care, had experienced episodes of status epilepticus. The highest frequency of these life-threatening episodes ranged from less than 1 per month to 11 to 20 per month (mode = 1 to 2 per month, n = 16).

All respondents reported that their child had been admitted to hospital (i.e., due to prolonged seizures, status epilepticus, or repetitive seizures). Other common reasons for hospitalization included: extended Electroencephalography recording, initiation of a ketogenic diet, immune system challenges, complications of a seizure, weaning off an anti-seizure drug or starting a new anti-seizure drug. The number of hospitalizations ranged from 3 to 500 (median = 25; n = 16). Other conditions reported as “frequent or severe” or “very frequent or very severe” by a majority of respondents were: developmental delay, repetitive behaviours, social disorders (including autism spectrum disorder), and movement disorders, including gait disturbances and ataxia.

Severe, prolonged seizures (a defining feature of Dravet syndrome), cause encephalopathy or brain injury. Catastrophic seizures steal skills, which leads to global delays in academic abilities, walking, and talking, and to autonomic dysfunctions. Every aspect of a child's life can be affected, including schooling, independence, social activities, friendships, mobility, health, safety, and financial and emotional aspects. Seizure control, especially if achieved early, may lead to better outcomes. Lack of seizure control has a devastating impact and a huge effect on quality of life. Caregivers describe life with Dravet syndrome as a roller coaster: stressful, heart-wrenching, socially isolating, and limiting, causing financial and marital difficulties and making overall family life difficult.

To reduce the frequency and duration of seizures, patients are prescribed numerous anti-seizure medications. The seizures are difficult to control, so multiple anti-seizure drugs are used. Side effects increase as more medications are added and as dosages are increased. The best combination for a patient is usually found by trial and error using available medications, but this can lead to false hope and subject patients to a wide range of emotions, causing behavioural issues and side effects. Every change requires a very careful, slow titration to adjust medications. Many treatments are ineffective and some anti-seizure medications are contraindicated in patients.

With Dravet spectrum disorders, the important thing is seizure control. With better seizure control, it is possible to plan events and activities and expect to carry them through. It is possible for the patient to retain what they have learned and to access that knowledge. When things are unpredictable, you hope to make it through a work day with no call from the school or, at least, no call to meet the ambulance at the hospital.

3. Related Information About the Drug Being Reviewed

Of the 16 survey respondents, 3 had a child younger than three years of age and none had experience with stiripentol. The expectations for stiripentol were that it will increase seizure control and decrease episodes of status epilepticus.

Out of 16 respondents, 13 had a person with Dravet syndrome in their care who was older than three years of age. Of these, 12 had experience using stiripentol and, of these, 67% reported benefits with the drug and 58% reported risks or side effects. Sixty-seven per cent (8 out of 12) respondents reported their child was on a combination of clobazam and valproate before stiripentol was added on. Eleven caregivers reported that their child was still taking stiripentol (92% retention rate). The length of time on stiripentol was from months (n = 2) to years (n = 9; range 2 to 12 years). One caregiver reported their child had taken stiripentol for a period of days, developed an allergic reaction (hives) and discontinued the drug.

The symptom that was best managed by stiripentol was seizure control. One respondent reported great improvement and achievement of seizure freedom and improved cognition, which permitted a return to school for the child and work for the parent. Another respondent reported improvement in tonic seizures, but continuance of myoclonic seizures, walking difficulty, and agitation; they were still happy with the results but had had higher expectations for the drug.

When improvement in tonic-clonic seizures was reported in the survey as either "moderate improvement" or "major improvement" (the two highest ratings on the 7-point scale [n = 7]), there were concomitant improvements reported in: the quality of life of the individual with Dravet syndrome (n = 7); visits to the emergency department (n = 6); admissions to hospital (n = 6); and quality of life for siblings (n = 6), parents (n = 6) and the family as a whole (n = 6). Two respondents reported their child became free from tonic-clonic seizures while taking stiripentol.

Side effects reported were loss of appetite, nausea, weight loss, lethargy, fatigue, sleepiness, aggressive behaviour, bone pain, sleep disorder, compromised immune system, and cognitive impairment. Some respondents reported a need to carefully adjust medications and dosages to achieve a balance that provided improved seizure control and which limited side effects to an acceptable level.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	April 24, 2014
Alerts:	Weekly search updates until September 17, 2014
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
1	(diacomit* or stiripent* or estiripent* or BCX 2600 or BCX2600 or BRN 1313047 or BRN1313047).ti,ot,ab,sh,rn,hw,nm.	671
2	49763-96-4.rn,nm.	471
3	1 or 2	671
4	*stiripentol/	112
5	(diacomit* or stiripent* or estiripent* or BCX 2600 or BRN 1313047).ti,ab.	356
6	4 or 5	364
7	3 use pmez	153
8	6 use oemezd	216
9	7 or 8	369
10	remove duplicates from 9	232
11	exp animals/	36214442
12	exp animal experimentation/ or exp animal experiment/	1775161
13	exp models animal/	1169672
14	nonhuman/	4279664
15	exp vertebrate/ or exp vertebrates/	35287740
16	animal.po.	0
17	or/11-16	37445075
18	exp humans/	28078239
19	exp human experimentation/ or exp human experiment/	335865
20	human.po.	0
21	or/18–20	28080313
22	17 not 21	9366345
23	10 not 22	184

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for search:	April 15 to April 22, 2014
Keywords:	Diacomit, stiripentol, epilepsy, SMEI, Dravet
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Study Design (Not Randomized)

1. Inoue Y, et al. Epilepsia. 2009 Nov;50(11):2362-8.
2. Inoue Y, et al. Epilepsy Res. 2014 May;108(4):725-31.

Study Design (Not Randomized, Mixed Population, No Separate Results for Dravet Syndrome)

3. Perez J, et al. Epilepsia. 1999 Nov;40(11):1618-26.

APPENDIX 4: ADDITIONAL EFFICACY AND SAFETY EVIDENCE FOR STIRIPENTOL IN THE TREATMENT OF DRAVET SYNDROME

1. Objective

To summarize the evidence for efficacy and harms of stiripentol used in conjunction with clobazam and valproate from prospective interventional trials in patients with Dravet syndrome that did not meet the selection criteria for inclusion in the systematic review.

2. Findings

One prospective interventional trial[29-31] was identified in which stiripentol was added on to clobazam and valproate in patients with Dravet syndrome. The trial did not meet the selection criteria for the systematic review because it was uncontrolled. Efficacy and harms data are available from this trial for up to 52 weeks of continuous stiripentol treatment (i.e., 12-week short-term period plus 40-week long-term administration period for patients in whom efficacy was confirmed during the short-term period). Only results from the 12-week short-term period are published.[29]

Study Characteristics

The trial[29,31] was a non-randomized, single-group, open-label trial that evaluated the efficacy, safety, and pharmacokinetics of stiripentol added on to clobazam and valproate in Japanese patients with Dravet syndrome. Bromide was permitted as concomitant therapy and diazepam was allowed as rescue medication. To facilitate the comparison of the results with the STICLO-France trial, patients were divided into a younger group (Group 1: 1 to 18 years; n = 20) and an older group (Group 2: 19 to 30 years; n = 4). Patients for whom efficacy was confirmed during the 12-week stiripentol fixed-dose period (i.e., those with ≥ 50% decrease in seizure frequency compared with baseline) were eligible for the long-term administration period where treatment was followed for up to 52 weeks.[30] Six patients who received stiripentol in conjunction with clobazam and valproate in a national clinical study were also included in the long-term administration period and were identified as Group 3. A detailed summary of the study characteristics is provided in Table 10.

TABLE 10: SUMMARY OF STUDY CHARACTERISTICS

Study ID	Design	Inclusion Criteria	N	Intervention	Duration	Primary End Point
Inoue et al.[29-31] (11 centres in Japan)	**Short-term period:** Multi-centre, single-group, uncontrolled, open-label trial including 4-wk baseline, 4-wk STP dose-adjustment, and 12-wk STP fixed-dose periods	Male and female pts, 1–30 yrs, diagnosed with DS, inadequate seizure control (≥ 4 clonic or tonic-clonic seizures per 30 days) with stable doses of CLO and VPA[a] for ≥ 4 wks during baseline period; BW ≥ 5 kg	24	Dose-adjustment period: STP 20 mg/kg/day titrated to 50 mg/kg/day (or 1,000 mg/day titrated to 2,500 mg/day if BW ≥ 50 kg) Fixed-dose period: STP 50 mg/kg/day or 2,500 mg/day if BW ≥ 50 kg	12 wks (fixed-dose period)	Responder rate (proportion of pts with ≥ 50% reduction from baseline in clonic or tonic-clonic seizures over last 4 wks of the fixed-dose period)
	Long-term period: 40-week open-label extension	Pts with confirmed efficacy during 12-week fixed-dose period, plus 6 pts who received STP continuously with a CLO and VPA regimen unchanged for ≥ 4 weeks in a national clinical study	27	As above for fixed-dose period	40 weeks	NR

BW = body weight; CLO = clobazam; DS = Dravet syndrome; NR = not reported; pts = patients; STP = stiripentol; VPA = valproate; wk = week; yrs = years.

[a] Doses were up to the maximum tolerated dose of 0.5 mg/kg/day for CLO, and 30 mg/kg/day for VPA.

The trial comprised five periods:

1. Baseline (4 weeks), in which patients were observed before receiving stiripentol
2. Dose adjustment (4 weeks), during which the dose of stiripentol was titrated until the maintenance dose was achieved
3. Fixed-dose (12 weeks), during which the maintenance dose of stiripentol was given
4. Long-term administration (40 weeks), a period of up to 52 weeks of treatment, including the fixed-dose period
5. Continuous evaluation, during which stiripentol was made available until approval.

Patient Characteristics

The mean age (± SD) of patients in Group 1 (aged ≤ 18 years) was 5.7 (± 4.3) years, and 22.8 (± 1.3) years in Group 2 (older than 18 years of age). Seventeen patients underwent genetic analysis for sodium channel voltage-gated type 1 (*SCN1A*); of these, 16 (94%) were found to have mutations, thus supporting the diagnosis of Dravet syndrome.

Patient Disposition

Twenty-seven patients were screened for entry into the baseline period. Of these, three patients (11.1%) dropped out during the baseline phase prior to receiving stiripentol in the dose-adjustment period: two patients were withdrawn due to low seizure frequency (less than 4 seizures per 30 days) and one patient was withdrawn due to protocol violation (use of prohibited concomitant drugs). Therefore, 24 patients entered the dose-adjustment period and all 24 completed the dose-adjustment and fixed-dose periods. For the long-term administration period, 21 patients entered from the fixed-dose period, in addition to six patients who had received stiripentol continuously in conjunction with clobazam and valproate in a national clinical study. Of these, three patients (11.1%) discontinued due to the following reasons: patient request, use of concomitant prohibited drugs or treatment, and investigator judgment.

Efficacy Outcomes

After 12 weeks of fixed-dose stiripentol added on to clobazam and valproate, the responder rate (i.e., patients with ≥ 50% reduction in the frequency of clonic or tonic-clonic seizures during the last four weeks of the fixed-dose stiripentol period, compared with the 4-week baseline period) was 65.0% in patients ≤ 18 years (Group 1) and 75.0% in patients older than 18 years (Group 2). The overall responder rate (groups 1 and 2 combined) was 66.7% (95% CI: 44.7; 84.4) in Groups 1 and 2 combined. There were four patients (three in Group 1 and one in Group 2) who were free from tonic-clonic seizures during this time period. Results by analysis group are reported in Table 11.

TABLE 11: SUMMARY OF EFFICACY OUTCOMES

Outcome	Group 1 (N = 20)	Group 2 (N = 4)
Seizure-free status (proportion of patients with no seizures after 12 weeks of fixed-dose STP), n (%) [95% CI]	3 (15.0) [NR]	1 (25.0) [NR]
Seizure frequency (proportion of responders[a] after 12 weeks of fixed-dose STP), n (%) [95% CI]	13 (65.0) [40.8; 84.6]	3 (75.0) [19.4; 99.4]

CI = confidence interval; NR = not reported; STP = stiripentol.
[a] Seizure reduction of ≥ 50% from baseline over last four weeks of fixed-dose phase.

For those patients with confirmed efficacy who were eligible to enter the 40-week extension, at the end of the long-term administration period (52 weeks including the fixed-dose period), the mean change (± SD) in frequency of clonic or tonic-clonic seizures (compared with the baseline period) in patients

≤ 18 years of age was –60.31% (± 35.29%), and was –40.51% (± 25.50%) in patients over 18 years of age. The change in seizure frequency for all types of epileptic seizures compared with baseline was –78.74% (± 21.26%) in patients ≤ 18 years of age. Results for all epileptic seizures were not provided for patients over 18 years of age.

Pharmacokinetics

At the end of the 12-week fixed-dose period, stiripentol plasma concentrations were 4 to 25 mcg/mL. Plasma concentrations of valproate and bromide did not appear to change from the baseline period, whereas plasma concentrations of clobazam (1.8-fold increase), and its metabolites: N-desmethyl-clobazam (2.3-fold increase) and 4'-hydroxy-N-desmethyl-clobazam (0.17-fold decrease) changed compared with the baseline period.

Harms Outcomes

Treatment-emergent adverse events (TEAEs) reported throughout the trial are summarized in Table 12. No deaths or withdrawal due to adverse events (WDAEs) occurred during any period of the trial. In groups 1 and 2 combined, severe TEAEs occurred in four patients (16.7%) up to 20 weeks (including the baseline, dose-adjustment and fixed-dose periods) and in nine patients (42.9%) up to the end of the long-term administration period (52 weeks). In Group 3, one (16.7%) patient experienced a severe TEAE during the long-term administration period. The most common TEAEs were somnolence, nasopharyngitis, anorexia, ataxia, diarrhea, upper respiratory tract inflammation, influenza, and gamma glutamyl transpeptidase (γ-GTP) increased.

TABLE 12: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS

Outcome	Short-Term (Up to 20 Weeks)	Long-Term (Up to 52 Weeks)	
	Group 1 + 2 (N = 24)	Group 1 + 2 (N = 21)	Group 3 (N = 6)
Any TEAE, n (%)	24 (100)	21 (100)	5 (83.3)
Severe TEAE , n (%)	4 (16.7)[a]	9 (42.9)[b]	1 (16.7)[c]
WDAE, n (%)	0 (0)	0 (0)	0 (0)
TEAE > 10% of pts, n (%)	Bronchitis 3 (12.5) Nasopharyngitis 11 (45.8) Anorexia 14 (58.3) Ataxia 13 (54.2) Somnolence 19 (79.2) Tremor 7 (29.2) URTI 4 (16.7) Diarrhea 6 (25.0) Dry skin 5 (20.8) AST increased 3 (12.5) γ-GTP increased 8 (33.3) Fall 3 (12.5)	Nasopharyngitis 12 (57.1) URTI 9 (42.9) Anorexia 8 (38.1) Diarrhea 7 (33.3) Hordeolum 4 (19.0) Influenza 4 (19.0) Fever 4 (19.0) Pneumonia 3 (14.3) Somnolence 3 (14.3) Conjunctivitis 3 (14.3) Thrombocytopenia 3 (14.3)	Nasopharyngitis 3 (50.0) Influenza 2 (33.3) Somnolence 2 (33.3)

AST = aspartate aminotransferase; γ-GTP = γ glutamyl transpeptidase; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract inflammation; WDAE = withdrawal due to adverse event.

[a] Four events: bronchitis (n = 2), fever (n = 1), status epilepticus (n = 1).

[b] Fifteen events: pneumonia (n = 3), anorexia (n = 2) and respiratory synctial virus infection, epilepsy, influenza, malnutrition, virus infection, status epilepticus, infection, bronchitis, fever, and a general physical health deterioration (n = 1 each).

[c] One event: convulsions (n = 1).

Limitations

The study is limited by an open-label design, lack of a control group, and small sample size. All seizure outcomes were recorded by patients' caregivers, therefore, reporting bias may have been introduced, as is also the case in the STICLO trials[18-20] included in the systematic review. Caregivers did receive training on counting and measuring seizures prior to initiation of the trial. The generalizability of the results to a Canadian population of patients with Dravet syndrome may be limited, as the trial was conducted only in Japanese patients. Data available from the long-term administration period were limited and the appropriateness of including six patients from another study in the long-term administration phase is questionable. Nonetheless, the results were reported by analysis groups and these six patients were not combined with those in groups 1 and 2. A limitation of all extension studies is that only those patients who responded to treatment were eligible for participation in the long-term phase. This is not a major concern, as there was a high participation rate (87.5%); however, this represents a select patient population with the highest likelihood of benefit and ability to tolerate treatment.

3. Summary

One open-label, uncontrolled, prospective interventional trial was identified that evaluated stiripentol added on to clobazam and valproate in patients with Dravet syndrome. The trial comprised five periods including baseline, dose-adjustment, fixed-dose, long-term administration, and continuous evaluation of stiripentol. Efficacy and harms were evaluated after the 12 week fixed-dose period[29,31] and after the long-term administration period of 40 weeks (i.e., up to 52 weeks of continuous stiripentol treatment).[30,31] After 12 weeks, fixed-dose stiripentol reduced the frequency of clonic and tonic-clonic seizures by ≥ 50% from baseline in 65.0% of patients aged ≤18 years (Group 1), and 75.0% of patients over 18 years of age (Group 2). For those patients with confirmed efficacy who were eligible to enter the 40-week extension, at the end of the long-term administration period, the mean ± SD change in frequency of clonic or tonic-clonic seizures (compared with the baseline period) in patients ≤ 18 years was –60.31% ± 35.29%, and –40.51% ± 25.50% in patients over 18 years of age. There were no deaths or WDAEs during the trial duration. The most frequent TEAEs associated with the combination of stiripentol, clobazam, and valproate over 52 weeks were somnolence, nasopharyngitis, anorexia, ataxia, diarrhea, upper respiratory tract inflammation, influenza, and γ-GTP increase. Given the uncontrolled, open-label design, the results from this trial should be interpreted with caution.

APPENDIX 5: EFFICACY AND SAFETY EVIDENCE FOR LEVETIRACETAM AND TOPIRAMATE IN THE TREATMENT OF DRAVET SYNDROME

1. Objective

To summarize the evidence for efficacy and harms of levetiracetam and topiramate as adjunctive therapy in patients with Dravet syndrome from prospective interventional trials.

2. Findings

Two trials each for levetiracetam[32,33] and topiramate[34,35] were identified in the published literature that investigated the efficacy and harms of each drug used as add-on therapy to existing antiepileptic drugs (AEDs) in patients with Dravet syndrome.

Study Characteristics

A detailed summary of the study characteristics is provided in Table 13.

All four trials included a baseline observation period of one to three months during which changes in existing AED therapy were not allowed. In keeping with the different inclusion criteria, patients who continued to experience seizures during baseline entered a titration period where either levetiracetam or topiramate was titrated to a maintenance dose. Following this, patients were evaluated or followed up for different periods of time, as detailed in Table 13. Three trials were conducted in patients with Dravet syndrome only, whereas the trial by Chhun et al., 2011[32] included 102 patients with refractory seizures, nine of whom had a diagnosis of Dravet syndrome. The mean age of children in most trials was approximately nine years. The majority of enrolled children (more than 50%) were on two concomitant AEDs to which levetiracetam (titrated to 40 to 60 mg/kg/day) or topiramate (titrated to 6 to 8 mg/kg/day) was added. The concomitant AEDs remained unchanged throughout the trials and included valproate, clobazam, lamotrigine, vigabatrin, topiramate, phenobarbital, clonazepam, stiripentol, nitrazepam, primidone, carbamazepine, felbamate, acetazolamide, and gabapentin. The most frequently used concomitant AED was valproate.

Patient Characteristics

The mean age of children across the trials was approximately nine years, with the exception of the trial by Nieto-Barrera et al., 2000[35] that enrolled older children (mean age 13.3 years). In the trial by Striano et al., 2007,[33] patients were required to have undergone genetic analysis for sodium channel voltage-gated type 1 (*SCN1A*) prior to entry; of these, 16 (57.1%) were found to have mutations, thus supporting the diagnosis of Dravet syndrome in those patients.

Patient Disposition

Overall, 42% (43 out of 102)[32] and 17.9% (5 out of 28)[33] of patients discontinued the two levetiracetam trials. The main reason for discontinuation in the Chhun et al., 2011 trial[32] was due to lack of efficacy (29 patients; 28%); in the Striano et al., 2007 trial,[33] it was due to adverse events (AEs) (5 patients; 17.9%). There were no patient discontinuations in the topiramate trials.[34,35]

Efficacy Outcomes

Data on reductions in seizure frequency associated with add-on levetiracetam and topiramate are provided in Table 14.

TABLE 13: SUMMARY OF TRIAL CHARACTERISTICS

Study	Design	Inclusion Criteria	N	Intervention	Mean Duration	Efficacy End Points
Levetiracetam Trials						
Chhun et al., 2011[32]	Open-label, single-group, multi-centre trial with 1-mo baseline, 1-mo titration, and 5-mo evaluation periods	Age 6 mo–15 yrs with resistant epilepsy (≥ 8 seizures per mo at a stable frequency during baseline), on 1–3 AEDs at stable dose for 1 mo, countable seizures (not defined)	102 RS, incl. 9 DS	LVT 10 mg/kg/day (20 mg/kg/day for < 2 yrs) added to BL therapy and titrated to 40 mg/kg/day (60 mg/kg/day for < 2 yrs)	6 mo	Seizure frequency after 3 and 6 mo of LVT, proportion of responders (> 50% reduction of seizures from baseline), seizure-free status
Striano et al., 2007[33]	Open-label, single-group, multi-centre, trial with 8-wk baseline, 5- to 6-wk up-titration, and 12-wk evaluation periods; 5- to 36-mo extension	Age ≥ 3 yrs with SMEI, ≥ 4 tonic-clonic seizures/mo during last 8 wks, previous use of ≥ 2 AEDs, mutational analysis for *SCN1A*	28	LVT 10 mg/kg/day titrated up to 50 to 60 mg/kg/day in two doses	12 wks	Responder rate by seizure type and reduction of the mean number per week of each seizure type at end of 12 wks Responders (> 50% and > 75% reduction from baseline and seizure free at 12 wks) were differentiated
Topiramate Trials						
Coppola et al., 2002[34]	Open-label, single-group, multi-centre trial with 3-mo baseline, 2-wk titration and follow-up to 24 mo	Age ≥ 12 mo with SMEI, ≥ 4 seizures per mo over 3-mo baseline period, use of 1–2 AEDs	18	TOP 0.5 to 1 mg/kg/day titrated up to 12 mg/kg day	11.9 mo	Response rated as seizure control (100% seizure free) or decrease in seizure rate at end of follow-up (mean 11.9 mo) compared with baseline and denoted as very good (50–98%) and minimal (< 50% with minimal change in seizure severity)

Study	Design	Inclusion Criteria	N	Intervention	Mean Duration	Efficacy End Points
Nieto-Barrera et al., 2000[35]	Open-label, single-group trial with 3-mo baseline, 3 titration schedules (duration of each not specified) and follow-up to 18 mo	Age 2–22 yrs with SMEI, use of ≥ 1 AED	18	TOP 0.5 to 1 mg/kg/day titrated up to 6 to 8 mg/kg/day using 3 different titration schedules	10.5 mo	Reduction in seizure rate at end of follow-up (mean 10.5 mo) compared with baseline Reductions in seizure rates of > 50%, > 75% and seizure suppression (100% seizure free) were differentiated

AED = antiepileptic drug; BL = baseline; DS = Dravet syndrome; incl = including; LVT = levetiracetam; mo = month; pts = patients; RS = refractory seizures; SCNA1 = sodium channel voltage-gated type 1; SMEI = severe myoclonic epilepsy of infancy; TOP = topiramate; wk = week; yrs = years.

TABLE 14: SUMMARY OF EFFICACY OUTCOMES

Outcome	Levetiracetam Trials		Topiramate Trials	
	Chhun et al., 2011 (N = 9)[a]	Striano et al., 2007 (N = 28)[b]	Coppola et al., 2002 (N = 18)[a]	Nieto-Barrera et al., 2000 (N = 18)[a]
Seizure-free status, n (%)	0 (0)[a]	3 (11)	3 (17)	3 (17)
Seizure frequency, n (%):				
≥ 75% reduction from BL	NR	11 (39)	9 (50)	9 (50)
≥ 50% reduction from BL	1 (11)	18 (64)	13 (72)	13 (72)
< 50% reduction from BL	8 (89)	10 (36)	5 (28)	5 (28)

BL = baseline; NR = not reported.
[a] Results are for all seizure types.
[b] Results are for tonic-clonic seizures; 11 out of 28 (39%) patients were responders (> 50% reduction from baseline) for at least two seizure types.

In Chhun et al., 2011,[32] after six months of add-on levetiracetam, only one of nine (11%) patients with Dravet syndrome experienced ≥ 50% reductions in seizures from baseline. No patient achieved seizure-free status in this trial. In the trial by Striano et al., 2007,[33] after 12 weeks of add-on levetiracetam, 39% of patients achieved ≥ 75% reduction in tonic-clonic seizures, 11% of patients were seizure free, and the percentage of patients with ≥ 50% reductions in seizures from baseline was 64%.

In Coppola et al., 2002[34] after a mean duration of approximately 12 months of add-on topiramate, 72% of patients experienced ≥ 50% reductions in seizures from baseline and 50% of patients achieved ≥ 75% reductions. In Nieto-Barrera et al., 2000,[35] similarly, 72% of patients achieved a ≥ 50% reduction in seizure rate and 50% of patients had a ≥ 75% reduction from baseline. In both trials, 17% of patients were seizure free after 11 to 12 months of add-on topiramate treatment.

Harms Outcomes

The treatment-emergent AEs (TEAEs) reported throughout the studies are summarized in Table 15. No deaths were reported during any of the trials and severe TEAEs were reported only in the trial by Chhun et al., 2011,[32] which included the largest sample of patients with refractory seizures. In general, the addition of levetiracetam or topiramate to conventional AEDs appeared to be well tolerated, although reporting of TEAEs, serious or severe AEs, and frequency of AEs was limited across the trials. The TEAEs reported were mainly neurological AEs (e.g., hyperexcitability, dizziness, sleepiness). WDAEs appeared to be higher with levetiracetam (4.9% to 18%) compared with topiramate (0% or not reported) in the trials.

TABLE 15: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS

	Levetiracetam Trials		Topiramate Trials	
Outcome	Chhun et al., 2011 (N = 102)[a]	Striano et al., 2007 (N = 28)	Coppola et al., 2002 (N = 18)	Nieto-Barrera et al., 2000 (N = 18)
Any TEAE, n (%)	48 (47)	2 (7)[b]	4 (22.2)[c]	NR
Severe TEAE, n (%)	6 (6)	NR	NR	NR
WDAE, n (%)	5 (5)	5 (18)[b]	0 (0)	0 (0)
TEAE > 10% of pts, n (%)	Hyperexcitability 22 (22) Sleep disorders 14 (14) Drowsiness 14 (14)	NR	None > 10%	NR

NR = not reported; pts = patients; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
[a] Harms results were reported in the total population only (i.e., patients with refractory epilepsy, which included nine patients with Dravet syndrome).
[b] It was stated LVT was well tolerated and that mild and transitory sleepiness or sedation occurred in only two patients; however, five patients withdrew due to AEs (irritability n = 2, cutaneous rash, worsening of myoclonic seizures, and thrombocytopenia n = 1 each).
[c] AEs reported were mild weight loss (< 5% of body weight), hypermenorrhea, renal microlithiasis, hyperoxia, nervousness, and transient dysarthric speech.

Limitations

All five trials are limited by open-label designs, lack of control or comparator groups, small sample sizes, and relatively short follow-up periods given the chronic nature of Dravet syndrome. Different titration schedules were used and final doses of levetiracetam or topiramate varied considerably across the trials, thus making comparisons difficult. Levetiracetam is not indicated for use in children in Canada; therefore, the appropriateness of the maintenance dose of levetiracetam used in the trials could not be verified. Although topiramate is not specifically indicated for use in Dravet syndrome in Canada, it is

indicated for use as adjunctive therapy for children two years and older with epilepsy who are not controlled satisfactorily with conventional therapy. The recommended dose of topiramate as adjunctive therapy in children is 5 to 9 mg/kg/day in divided doses. Therefore, the maintenance dose of topiramate (12 mg/kg/day) used in Coppola et al., 2007[34] would be considered higher than recommended, whereas the dose (6 to 8 mg/kg/day) used in Nieto-Barrera et al., 2000,[35] would be in keeping with the recommended dose in Canada. Patients were also on a wide variety of concomitant AEDs to which levetiracetam or topiramate were added, thereby confounding meaningful interpretation of the results. As in the STICLO trials,[18-20] seizure type and frequency were recorded by parents and caregivers at home and at school; therefore, reporting bias may have occurred. Harms data were poorly reported in the trials, with the exception of one trial;[32] however, the results were reported for a mixed population of patients with refractory seizures and not specifically for patients with Dravet syndrome; thus, the generalizability of the overall results of this trial to patients with Dravet syndrome is unclear. Lastly, mutational analysis for *SCN1A* was conducted in one trial only (Striano et al., 2007[33]), and only 57% of patients were found to have mutations. Therefore, it is possible that patients may not have had a definitive diagnosis of Dravet syndrome, although the diagnosis was primarily based on clinical criteria and the presence of the *SCN1A* mutation is not specific for Dravet syndrome.

3. Summary

Four published, open-label, uncontrolled, prospective interventional studies were identified that evaluated (in two trials each) the addition of levetiracetam[32,33] or topiramate[34,35] to existing AED therapy in patients with Dravet syndrome. For add-on levetiracetam, after six months of treatment in one trial, one of nine (11%) patients with Dravet syndrome experienced ≥ 50% reductions in seizures from baseline, and no patient achieved seizure-free status. In the other trial, after 12 weeks of add-on levetiracetam, 39% of patients achieved ≥ 75% reduction in tonic-clonic seizures from baseline, 11% of patients were seizure free, and the percentage of patients with ≥ 50% reduction in seizures from baseline was 64%. For add-on topiramate, in both trials, after approximately 11 to 12 months of treatment, approximately 72% of patients experienced ≥ 50% reductions in seizures from baseline and 50% of patients achieved ≥ 75% reductions. In both trials, 17% of patients were seizure free after 11 to 12 months.

The reporting of harms data was limited among the trials. The TEAEs reported were mainly neurological (e.g., hyperexcitability, dizziness, sleepiness) and WDAEs appeared to be higher with levetiracetam (4.9% to 18%) compared with topiramate (0% or not reported). Overall, while it appears that add-on levetiracetam or topiramate provide reductions in seizure frequency compared with baseline frequency in patients with Dravet syndrome, the open-label designs, lack of control groups, and small sample sizes in the trials, coupled with uncertainty as to the appropriateness of the doses used and confounding nature of the background AED therapy, warrants that the results from these trials be interpreted with caution.

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