CDEC FINAL RECOMMENDATION

STIRIPENTOL
(Diacomit — Biocodex SA)
Indication: Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome)

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that stiripentol be listed for use in combination with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (Dravet syndrome), whose seizures are not adequately controlled with clobazam and valproate alone, if the following conditions are met:

Conditions:
- Patient is under the care of a neurologist.
- Reduction in price to improve the cost-effectiveness to an acceptable level.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) (STICLO-France [N = 42] and STICLO-Italy [N = 23]) demonstrated that treatment with stiripentol, in combination with clobazam and valproate, resulted in statistically significant and clinically meaningful reductions in seizure frequency in patients with Dravet syndrome.
2. Based on the CADTH Common Drug Review's (CDR) estimated incremental cost per quality-adjusted life-year (QALY) of $104,491 for stiripentol, CDEC concluded that stiripentol is not a cost-effective treatment option at the submitted price ($6.37 per 250 mg and $12.73 per 500 mg capsule or sachet).

Background:
Stiripentol is indicated for use in combination 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. Stiripentol is available as capsules or powder for suspension, 250 mg or 500 mg, and the recommended dose is 50 mg/kg/day, which may be divided into 2 to 3 doses per day.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs of stiripentol, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients and caregivers.

Patient Input Information
The following is a summary of information provided by one patient group that responded to the CDR call for patient input.

- Dravet syndrome is a catastrophic form of epilepsy; seizures are severe and difficult to control. Every aspect of a child's life can be affected including schooling, independence, social activities, friendships, family relationships, mobility, safety, and emotions.
- Dravet syndrome is often accompanied by developmental delay and conditions (including autism spectrum disorders) that cause social and behavioural problems, and difficulties with movement.
- Dravet syndrome is also catastrophic for families. Siblings of children with the syndrome routinely fear for their brother or sister and sometimes feel overlooked. Parents frequently experience strains on their marriage and sometimes marriage breakdown as well as financial hardship and unrelenting stress.
- Multiple anti-seizure drugs are used for seizure control and adverse effects increase as more medications are added and as dosages are increased.

Clinical Trials
The CDR systematic review included two double-blind, placebo-controlled RCTs of patients with Dravet syndrome: STICLO-France (N = 42) and STICLO-Italy (N = 23). 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, and 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), 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 open-label stiripentol therapy in all study participants (plus clobazam and valproate).

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Seizure-free status — the proportion of patients who were free of seizures during the second month of the double-blind treatment period.
- The proportion of responders — children who did not meet any of the following non-responder criteria:
  - after two months of treatment, the number of generalized clonic or tonic-clonic seizures during the second month of the double-blind period, had not decreased by ≥ 50% compared with the number of seizures during the baseline period
  - withdrawn from the study because of the occurrence of status epilepticus
  - number of seizures had increased by ≥ 50% compared with the baseline period, within a 0 to 20 day period after entry into the double-blind period
  - increase of > 50% in the number of seizures during the baseline period compared with the period before baseline; and during the first month of the double-blind period, the number of seizures did not return to the previous number before the baseline period.

- The percentage of children with ≥ 50% decrease from baseline in seizures during the second month of double-blind period.
- Number of tonic-clonic seizures in the double-blind period versus baseline.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The proportion of responders during the double-blind period was the primary outcome in both studies.

Efficacy

- 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 clonic or tonic-clonic seizure (*P* values not reported).
- The percentage of responders was statistically significantly greater in the stiripentol groups compared with placebo:
  - STICLO-France: 15 patients (71.4%) with stiripentol versus 1 (5.0%) with placebo; between-treatment difference 66.4% (95% confidence interval [CI], 42.2% to 85.7%).
  - STICLO-Italy: 8 patients (66.7%) with stiripentol versus 1 (9.1%) with placebo; between-treatment difference 57.6% (95% CI, not reported).
- The percentage of children with at least a 50% decrease in seizures during the second month of the double-blind period was statistically significantly greater in the stiripentol groups compared with placebo:
  - STICLO-France: 15 patients (71.4%) with stiripentol versus 1 (5.0%) with placebo ($P < 0.00002$).
  - STICLO-Italy: 8 patients (73%) with stiripentol versus 1 (11%) with placebo (*P* not reported).
- The improvement in the number of seizures from baseline was greater in the stiripentol groups compared with the placebo groups during the first month of the double-blind period:
  - STICLO-France: 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 ($P < 0.001$ between groups).
  - STICLO-Italy: 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 ($P < 0.05$ between groups).
- The improvement in the number of seizures from baseline was also greater in the stiripentol groups compared with the placebo groups during the second month of the double-blind period:
  - STICLO-France: the number of seizures decreased from 17.9 to 5.2 in the stiripentol group and from 18.5 to 13.8 in the placebo group ($P < 0.002$ between groups).
  - STICLO-Italy: the number of seizures decreased from 33.6 to 9.8 in the stiripentol group and from 27.4 to 16.7 in the placebo group (difference not significant).

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - STICLO-France: 28.6% with stiripentol and 15% with placebo.
  - STICLO-Italy: no serious adverse events were reported.
- The proportion of patients who reported at least one adverse event was reported as follows:
  - STICLO-France: 100% with stiripentol and 45% with placebo.
  - STICLO-Italy: 83% with stiripentol and 27% with placebo.

- The proportion of patients who withdrew due to adverse events was reported as follows:
  - STICLO-France: 4.8% with stiripentol and 10% with placebo.
  - STICLO-Italy: 8.3% with stiripentol and 0% with placebo.
- The most frequently reported adverse events in the stiripentol group in STICLO-France included drowsiness, appetite loss, and weight loss; in STICLO-Italy, patients in the stiripentol group were more likely to report sleepiness, behaviour disorders, and appetite loss.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis based on a Markov model over a five-year time horizon, in patients with Dravet syndrome whose seizures are not adequately controlled with the combination of clobazam and valproate. The target population was based on the baseline characteristics of patients in the STICLO-France and STICLO-Italy trials. The model was comprised of 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 among the health states were obtained from the STICLO-France and STICLO-Italy trials. Transition probabilities to the death state were derived from the DIAVEY study. Costs included medication costs, change of therapy costs, costs associated with seizure status, and costs used to manage status epilepticus. Utility values were obtained from a study of Lennox-Gastaut syndrome, a form of epileptic encephalopathy that the manufacturer considered comparable with Dravet syndrome. The manufacturer reported that the incremental cost-utility ratio (ICUR) for stiripentol as adjunct to clobazam and valproate was $50,122 compared with clobazam and valproate alone.

CDR identified the following key limitations with the manufacturer's pharmacoeconomic evaluation:

- The manufacturer assumed that all patients in the comparator group (i.e., clobazam and valproate alone) are in the NAC state (< 50% reduction in seizure frequency) and can transition only to the death state. Based on evidence from STICLO-France and STICLO-Italy, between 5% and 9.1% of patients receiving clobazam and valproate alone achieved a reduction of at least 50% in the number of seizures. CDR examined the impact of varying the distribution of patients in the NAC and NSF health states in the clobazam and valproate alone group.
- Utility values were based on a conference abstract from a study of Lennox-Gastaut syndrome. CDR considered alternate utility values.
- The model did not adjust for the expected weight increases and corresponding dose adjustments that are inherent with patient growth over a five-year time horizon. CDR considered alternate patient weights.
- The model assumed that the efficacy of stiripentol at two months was maintained over five years and did not consider potential waning of treatment effect. The manufacturer's model did not allow re-analysis to assess the impact of this assumption.
- The manufacturer assumed that patients on stiripentol who were NAC after 2 months of treatment would return to clobazam and valproate alone. According to clinical expert opinion, patients with Dravet syndrome are expected to receive stiripentol for 3 to 6 months before clinical assessments are made regarding efficacy with stiripentol. CDR calculated the

cost of treatments for the first year to include 4 months of stiripentol treatment (instead of 2 months).

When accounting for these limitations, CDR found that the ICUR for stiripentol as adjunct to clobazam and valproate compared with clobazam and valproate alone ranged from $51,160 to $120,419 per QALY gained, with a most likely estimate of $104,491 per QALY gained.

At the submitted price ($6.37 per 250 mg capsule or sachet and $12.73 per 500 mg capsule or sachet), treatment with stiripentol would cost an additional $38.20 per patient per day (based on a body weight of 30 kg) in addition to clobazam (0.5 mg/kg/day to 1 mg/kg/day, maximum 40 mg daily, $0.01 to $0.44 daily) and valproic acid (15 mg/kg/day to 60 mg/kg/day, $0.27 to $1.43 daily).

Other Discussion Points:

CDEC noted the following:

- The dose of clobazam was lower than the recommended dose used in Canadian clinical practice. Stiripentol increases the plasma concentration of both clobazam and norclobazam, the active metabolite of clobazam, which may have influenced the efficacy of stiripentol observed in the included studies. The extent of the clinical benefit of stiripentol as adjunctive therapy in patients receiving clobazam at a dosage more reflective of that used in Canada is uncertain.
- Stiripentol inhibits cytochrome P450 isoenzymes; therefore, plasma concentrations of other antiepileptic medications should be monitored and doses may require adjustment.
- The included studies had small sample sizes and were conducted without power calculations; however, Dravet syndrome is a rare condition making it challenging to recruit patients.
- The validity and reliability of using a diary by parent or caregiver to record patient's seizure frequency is uncertain.

Research Gaps:

CDEC noted that there is limited evidence or an absence of evidence regarding the following:

- Direct comparison of stiripentol with other active potential adjunctive treatments.
- Long-term efficacy and safety data for the use of stiripentol.
- Data on the impact of stiripentol on status epilepticus, health care utilization, health-related quality of life, psychomotor development, and mortality.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

September 17, 2014 Meeting
Regrets:

One CDEC member could not attend this portion of the meeting.

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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