Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Stiripentol (Diacomit) for the treatment of seizures in patients with Dravet syndrome.
Name of patient group	Dravet.ca
Name of primary contact for this submission:	Patti Bryant
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1.1 Submitting Organization

dravet.ca is the Canadian Network for families, friends and caregivers of people with Dravet spectrum disorders**.**

dravet.ca will educate our 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 will receive and maintain a fund or funds and will apply all or part of the principal and income therefrom, from time to time, to qualified donees as defined at section 149.1(1) of the Income Tax Act (Canada).

dravet.ca will undertake activities ancillary and incidental to the attainment of the above charitable purposes.

1.2 Conflict of Interest Declarations

a) *We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:* Biocodex was a sponsor of the **2012 Dravet.ca Family, Physician and Researcher Conference**.
Sponsorship provided $10,000.

b) *We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:* n/a

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

We conducted an online survey of caregivers (family members) who have a child with Dravet syndrome from November 4 - 16, 2013.

Information about the survey was shared on our website, dravet.ca, Twitter account and Facebook page. We also shared information about the survey with 2 national epilepsy associations, the Canadian Epilepsy Alliance and the Canadian League Against Epilepsy, and asked them to pass the information along to their members and families affected by with Dravet syndrome. Survey responses were received from 19 caregivers (16 Canadians; 3 from outside Canada) who have a family member with Dravet syndrome. Only the caregiver responses from Canadians were analyzed for this submission.

2.2 Impact of Condition on Patients

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.

ALL of the survey respondents reported that their family member with Dravet syndrome had experienced **tonic-clonic** (grand mal) seizures. The reported frequency of tonic-clonic seizures was:

- Lowest frequency range (n=16): less than 1 per month to 13-20/month (mode = < 1/month)
- Highest frequency range (n=16): 1-4/month to 350/month (mode = > 50/month)

In addition to tonic-clonic seizures (100% of respondents), 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%; 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 per month ranged from less than 1/month to 11-20/month (mode = 1-2/month, n=16).

ALL respondents reported that their child had been **admitted to hospital**. Prolonged seizures, status epilepticus or repetitive seizures was a reason for hospital admission among 100% of respondents. Other common reasons included: extended EEG recording, initiation of the Ketogenic diet, immune system challenges, complications of a seizure, and to wean off an anti-seizure drug and/or start a new anti-seizure drug. The number of hospitalizations ranged from 3 to 500 (median = 25, n=16).

In addition to seizures, **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.

The severe, prolonged seizures, a defining feature of Dravet syndrome, cause encephalopathy or brain injury. In other words, catastrophic seizures steal skills. Loss of skills leads to global delays in everything from academic abilities, through walking and talking, through to autonomic dysfunctions. Seizure control, especially if achieved early in the course of the disorder, may lead to better outcomes. Lack of seizure control has a devastating impact on the individual with Dravet syndrome, their parents and siblings.

The impact of Dravet syndrome in the words of the parents/caregivers who responded to our survey:

“It has changed our life so much, we need to watch our son and we are always trying to keep him from having a seizure. The most difficult part is when he is ill or the fact that heat is a trigger, it's keep us from being outside and he loves to be outside.”

“Devastating”

“He has had developmental delays that has reduce the number of friends of his own age and restricts what he can do for activities.”

“It has affected our child's freedom, independence, severe learning disabilities.”

“I hate that her day is lived in fear of a seizure and that she is not able to do some of the things that other kids can do all because of the what if.”

“affects every aspect of my son's life, schooling, independence, social activites, friendships, mobility, health, safety, financial, emotional”

“She went from being a bright, happy, active and inquisitive two year old, hitting or exceeding all developmental benchmarks, to being a globally delayed eighteen year old with the abilities of an eighteen month old during bad patches, to those of a four year old during her good spells.”

“The effects have been and will continue to be catastrophic”

“Dravet doesn't define her at all but it sure has affected her and everyone around her. Dravet syndrome sucks!”

“There has been a huge life change. The things most people take for granted do not apply for us. As our daughter gets older it seems to get harder instead of easier. A simple outing is not so simple and a lot of time it just dose not seem to be worth it to go.”

“Our child with dravet syndrome essentially must live in a bubble since anything can essentially cause a seizure that in turn could potentially end her life…Our child has had seizures that has stopped her from breathing and caused her to go on life support. The seizures can last over 2 hours. Our daughter was tube fed at 6 months of age. She was put on many drugs and essentially became a zombie.”

“She needs to be fed, dressed, bathed, diapered ...totally dependant on family and caregivers.”

“It has been very tough. There have been a lot of tears, guilty feelings, anger and love. <name removed> is dependant on us for every aspect of his daily care. He is completely non-verbal, has a wheelchair, has a feeding tube, had brain surgery, is waiting for feet surgery, been up and down off meds more times than I can remember and more.”

2.3 Patients’ Experiences With Current Therapy

To try and reduce the frequency and duration of seizures, patients are prescribed anti-seizure medications. The seizures are difficult to control, so multiple anti-seizure drugs are used. The side-effects increase as more medications are added and as dosages are increased. Trial and error with available medications is how the best combination is found for each patient. Every change requires a very careful, slow titration to adjust medications. Some anti-seizure medications are contraindicated for patients Dravet syndrome.

“multi drug therapies had little success, and the trial and errors where very difficult as it gave us false hope and also put him through a wide range of emotions, behavior, and side effects”

“Keppra, Zarontin: did not do anything at all, just side effects Phenobarbital: helped a bit but with a lot of side effect Tegretol, Dilantin: aggregated seizures Neurologists need to be better educated and learn to listen to caregivers for any treatment options to work. When I reported

that my child seizures were still so bad on Tegetol and Dilantin, and I suspected the drugs not helping and might be aggregating seizures, I was told firmly by our first neuro that drugs won't cause seizures and she wouldn't listen to me."

"we have been on the keto diet for 4 yrs. this eliminated prolonged seizure activity."

"early diagnosis, and referrals to centres that deal with this would have avoided years of pain and suffering for my son, and for us as a family"

"We almost lost him with the keto diet twice. He was given drugs that increased his seizures. Other times they work for a bit and then stop for some reason. The side effects of the drugs are the worst. You end up having to take other drugs to counteract the side effect of the one that may work for seizures."

"The Ketogenic diet has completely changed my sons life, he is doing so much better! It's been a blessing to our family but requires a lot of work, time and extra money. He is doing so well currently after being on the diet for 4 months."

"When he was on triliptial and lamotrigine, was having so many seizures we lost track"

"Epival, Topamax: reduced seizure frequency and length. Clobazam: helped with myoclonic seizure"

"Many unsuccessful drug trails."

"CBD - A lot of benefits. Talking more, sleeping better, less aggressive seizures, and eating much better. Rubbing extra CBD on gums during a seizures can stop the seizures (although it only stops the little, less aggressive ones for us)."

"Clozapan she would go into a rage"

"The drugs to stop seizures before diagnosis did more damage then the actual syndrome."

"Treatments all came with debilitating side effects. Tiredness, nausea, agitation, sleeplessness, loss of appetite, depression, constipation, sadness, lack of ability to concentrate, weight gain, weight loss"

"Keppra Dilentin Vimpat has been very affectve for her"

"Topamax - no benefits, caused anorexia and delayed speech. Clobazam- no benefits. Caused swallowing problems. Keppra- no benefit. Phenobarbital - no benefit. Vitamin B6 - no benefit"

2.4 Impact on Caregivers

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 be able to access the 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.

"Broken family,,,,,,,Bullied,,,,,,,no support in school,,,,,,,family and friends withdraw ,,,,,,,financial,,,,,, There is no world or phrase to explain how hard it is"

“It was a roller coaster life. It was hard to watch your child suffer without effective treatment. I also felt guilty of ignoring my other child's needs. It also affected marriage, my social life and my career.”

“This is really tough to put into words... Dravet syndrome has changed me and family in every way imaginable. Life with Dravet is stressful, heart wrenching and scary. My favourite moments are those when my daughter smiles and laughs…My heart is no longer at peace. It's totally broken. Im not sure if this heartache ever goes away. I try to stay strong, and optimistic.”

“Would not wish this on anyone”

“As a family we have become socially isolated. Our families for the most part don't get [it] and are now starting to leave us out of "family" events. What other families consider normal are impossible or exceptional for us (like vacations). Stress is unbelieveable”

“it makes it very hard for us to live outside of our house - do things as a family.”

“We had too live within 5 minutes from our hospital.”

“It has completely changed our lives, have become more isolated, more limitations, less travel, giving up careers.”

“We need to sleep with her at night to monitor seizures…Difficult financially...and always been a challenge with the extra costs and only one pay check. Difficult on marriage. Younger sibling loves her older sister dearly....been a difficult road for her as well.”

“Dravet syndrome means that we cannot plan anything, I missed my brother's wedding and lost the price of the plane fare… The unpredictability of the seizure activity is what truly upsets our lives. And the very real possibility of death”

“My other children have been through a lot, but have always been right beside their brother helping us out…On the other hand there has been some resentment, anger and depressed feelings because their lives have been affected by the lack of a "normal" life with a younger brother; my oldest especially as he had plans to teach soccer and coach the teams as he had finally gotten his wish to have a brother.”

“I have two sons, one older, one younger than she is…They have grown up with a constant fear in their home…waiting for a seizure to strike, and constantly aware that she could die for no reason, or simply from tipping over when in a dangerous spot (e.g. concrete floor, seven stairs at the front door). At one point, she lost all her skills except her pencil grasp and she remembered her blankie (she forgot everybody and everything else). She had to re-learn everything from crawling/walking, to remembering her people, to remembering the fact she liked music. Her older brother experienced that hell with me, that has left a mark on his soul.”

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

Information was obtained via an online survey as described in section 2.1.

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had to Date With the New Drug?

a) *Based on no experience using the drug:* Three out of 16 survey respondents (3/16) had a child under 3 years of age. None of these families had experience with stiripentol. The expectations for stiripentol were that it will increase seizure control and decrease episodes of status epilepticus.

b) *Based on patients' experiences with the new drug as part of a clinical trial or through a manufacturer's compassionate supply:* Thirteen out of 16 respondents had a person with Dravet syndrome in their care who was 3 yrs of age and over. One survey was incomplete, with no information related to treatments. **ALL other respondents (n=12) had experience using stiripentol**. Eleven caregivers reported that their child was still taking stiripentol (92% retention rate). The length of time on the medication was months (n=2) to years (n=9; range 2-12 years). One caregiver reported that their child had taken stiripentol for a period of days, developed an allergic reaction (hives) and discontinued the drug.

The symptom best managed by stiripentol was seizure control.

"STP has greatly improved our lives by achieving seizure freedom. We can now feel comfortable with my son attending school, and we see great progress year to year in his cognition. my husband and I can work again, and that eases the finanancial burden of a special needs child. It has also improved the relationship between spouse and siblings, to not live in a high stress, disfunctional family who is always on the alert for seizures."

"While the tonic seizures have stopped, we continue to deal with myoclonics and his walking is not the greatest, more off balanced than before and he does seem more agitated. That being said, we have been happy with the results, we were just hoping for more progession in his ability to walk, interact, feed himself etc. Maybe expectations were too high"

When improvement in tonic-clonic seizures was reported as either "moderate improvement" or "major improvement", the 2 highest ratings on our 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 family as a whole (n=6). Two respondents reported that 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.

"Her loss of appetite affected her so much she lost about fifty of her eighty five pounds. She was not well overall. We eventually found a good dosage that lessened seizure activity and still allowed her to eat."

"We "experimented" with the dose and the doses of other meds for about 12 months"

"we allow daily nap times at school and at home to help him make it through the day"

"We feel the seizure improvement outweigh the stiripentol side effect, so we take the side effects."

Section 4 — Additional Information

A compilation of the survey data and summary tables are attached.