

CADTH COMMON DRUG REVIEW

Patient Input

TEDUGLUTIDE (Revestive)

(Shire Pharmaceuticals Ireland Limited)

Indication: Short Bowel Syndrome (SBS), pediatrics

CADTH received patient input from:

Gastrointestinal Society

April 23, 2019

Disclaimer: The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations.

CADTH does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	Revestive® (teduglutide) for short bowel syndrome, pediatric
Name of the Patient Group	Gastrointestinal Society
Author of the Submission	██████████
Name of the Primary Contact for This Submission	██████████
Email	██████████
Telephone Number	██████████

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

As the Canadian leader in providing trusted, evidence-based information on all areas of the gastrointestinal tract, the GI (Gastrointestinal) Society is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to health care, and promoting gastrointestinal and liver health.

Canadian health care professionals request more than 600,000 of our BadGut® Basics patient information pamphlets each year, and tens of thousands of Canadians benefit from our important quarterly publication, the *Inside Tract® | Du coeur au ventre*^{MD} newsletter.

Our free BadGut® Lectures from coast to coast cover various digestive conditions for patients, caregivers, and other interested individuals. We also have dynamic websites in English (www.badgut.org) and French (www.mauxdeventre.org), which has had more than 3,600,000 *unique visitors* in the past 12 months, and almost 5 million visits. Organized on a number of topics, GI Society support group meetings offer a wealth of information for those newly diagnosed with a gastrointestinal disorder, as well as those who have lived with a condition for years.

Our highly trained staff and volunteers offer additional patient resources, including responding to information requests and participating in community initiatives. Staff and advisors work closely with health care professionals, other patient groups, and governments at all levels on behalf of GI patients. The GI Society, along with its sister charity, the Canadian Society of Intestinal Research (founded in 1976), has supported a number of significant clinical, basic, and epidemiological GI research.

Information Gathering

*CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how***

many patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

Information was obtained through telephone interviews and email communication with health care professionals working with children who have short bowel syndrome. This included a nurse practitioner lead in the Revestive® pediatric clinical trial, based in Toronto, and a hospital pharmacist working directly with short bowel syndrome pediatric patients. I also spoke with the parent of a child involved in the Revestive® clinical trial for close to two years. We have already published information on short bowel syndrome, which we gathered from medical studies and experts. A deeper understanding came from the Short Bowel Syndrome Oley Conference Roundtable in the US, which I participated in during 2015 and had an opportunity to discuss issues with several other short bowel syndrome patients and caregivers, and this informed our submission for the adult indication for Revestive® in 2015.

2. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Short bowel syndrome (SBS) is a potentially fatal gastrointestinal condition in which patients are unable to absorb sufficient nutrients and fluids through the intestines. It occurs when the small intestine doesn't function properly due to birth defect, trauma, disease, or when too much intestine is surgically removed.

In speaking with caregivers and health care providers with direct contact, we learned some heart-wrenching facts about infants and children with SBS. The majority of infants presenting with SBS to Canadian clinics are born with inadequate bowel, and a smaller number have Hirschsprung's disease, mitochondrial disease, focal muscular atrophy (FMA) syndrome, Crohn's disease, necrotizing enterocolitis, traumatic injury, surgery, gastrointestinal cancer, perforated bowel, blocked or restricted blood flow to the bowel, or congenital abnormalities.

In children, the symptoms and severity vary according to the part of the intestine that has been removed, as the small intestine is not identical in composition through its entire distance. Different sections of the small intestine are responsible for different nutrient absorption. As such, patient experiences can vary. Common symptoms include vitamin and mineral deficiencies, frequent diarrhea, extreme fatigue, cramping, dehydration, failure to thrive, and weight loss. Complications of these can include peptic ulcer disease, kidney stones, gallstones, small bowel bacterial overgrowth, and metabolic bone disease. In children, these symptoms and complications are much more dramatic and have dire social consequences in addition to the physiological ones.

Fatigue

The fatigue brought on by malnourishment restricts patients from participating in childhood activities such as play, school, self-care, and most social activities. In addition to the cumbersome feeding equipment, fatigue and abdominal pain likely reduces the ability of children with SBS to go to school normally. Missing school too often can have devastating effects on their lives, as they can fall behind on their studies. In addition, symptoms make it difficult for these children to participate in normal social functions.

Inability to Eat

Since short bowel syndrome patients are not able to digest food and fluids properly, their ability to eat normal foods and beverages can be profoundly impaired. Not only do they miss out on the taste and texture of foods, they also cannot fully participate in social interactions because many gatherings and holidays are centered around food or occur in restaurants. For children, this can be an isolating experience, as others their age share food and can find it difficult to understand why the child with short bowel syndrome has to miss out. On the other hand, these children can also consume large quantities of food because there is poor absorption. This leads to voluminous ostomy output. An ostomy involves a change in the way that urine or stool exits the body through the use of a surgical procedure. Bodily waste is rerouted from its usual path because of malfunctioning parts of the urinary or digestive system and waste material is collected in a pouch attached to the surface of the skin on the abdomen.

Mental Health Problems

Living with SBS can cause significant stress, anxiety, and depression. Social interactions can be restricted due to medical limitations and fatigue. This can result in isolation and reduce access to support networks.

3. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Treatment is determined upon the individual needs of the patient. Many will need to use a combination of therapies. These include:

Dietary Adjustments

A dietitian will devise and monitor customized menus and eating plans for each patient's individual medical needs. In some cases, individuals need to ingest exceptionally large meals 5-7 times a day because they cannot digest the amount of nutrients they require from regular meals. Other dietary adjustments may need to be made for the consumption of protein sources, carbohydrates, and fluids. However, specialized meals can be difficult and time-consuming to prepare. Nutritional supplements and formulas can also be expensive. Even with dietary adjustments, the individual will still suffer from insufficient nutrient and mineral absorption. These children are allowed to eat large quantities of foods, yet their liquid consumption is severely restricted. This means that the children have frequent foul-smelling bowel movements with undigested food.

Total Parenteral Nutrition

In children, early treatment is vital. If they do not experience growth of the bowel when they are young, then it is more likely that the gut will never function properly. This can lead to failure of the organs associated with digestion as, with lack of use, they will atrophy. This condition is most often managed by a specialized diet of total parenteral nutrition (TPN). This is an intravenous administration, typically via a central line, of nutrients into the bloodstream that contains amino acids (protein) and lipids (fats) in concentrated forms, carbohydrates, electrolytes (e.g., sodium and potassium), vitamins, and trace elements (e.g., copper and zinc). While this is a short-term life-preserving solution, it really amounts to toxic food for children that can over-stress their delicate systems, especially in infants.

Children with SBS feel thirst and their bodies cry out for water, but many can only consume a drop or two. One health care profession said a child in the trial cries because he is always thirsty and his daily maximum oral consumption of liquids is too low to satiate his thirst. This has a psychological effect and, over time, can make learning to respond to thirst in a normal route unattainable, with life-time consequences if not addressed early. All of these effects cause the child with short bowel syndrome to live a life relegated to hospital stays, carrying around a "backpack" pump, brain development delays, and delayed or deficient socialization.

Enteral Nutrition

Sometimes the children have a combination of TPN and enteral nutrition (ET), which is feeding that uses the gastrointestinal (GI) tract to deliver part or all of a person's caloric and nutritional requirements. It can include a normal oral diet, the use of liquid supplements, or delivery of part or all of the daily requirements by use of a gastrostomy tube (also called a G-tube). This is a tube inserted through the abdomen that delivers nutrition and hydration directly to the stomach. Patients might need to do this three times a day, and sometimes it must be repeated, as children are very likely to vomit with this kind of forced feeding. Therefore, these costly preparations are wasted and the child is fatigued with G-tube feeding and then vomiting, so this process can take a long time. TPN and ET equipment and formulas are often heavy and cumbersome and they must go through the surface of the skin, making the infant or child susceptible to dangerous infection. This means that the child is typically confined to hospital or frequently must be in hospital to receive nutrition. Feeding this way is important to help maintain the absorptive properties of the remaining intestine, but patients must have a partially functioning GI tract in order for this to be effective.

This therapy can be difficult to manage as blockages in the feeding tubes occur often. Bacterial contamination in the tube can cause serious infections.

Gastrointestinal Side Effects

Gastroesophageal reflux disease (GERD) occurs frequently with enteral feeding. Symptoms such as abdominal bloating, cramps, nausea, diarrhea, and constipation are also common. Re-feeding syndrome can also occur. This causes a large increase in insulin levels which leads to a dramatic increase in oxygen consumption, and increased respiratory and cardiac demand.

Surgery

There are a few surgical procedures that have been devised to increase the absorptive properties of the intestine. These involve artificially lengthening the intestine. Small bowel transplantation is sometimes attempted. However, complications from these surgeries can be severe and life threatening. Patients may require frequent hospitalizations due to infections and transplantation may cause serious damage to the liver or gallbladder.

4. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Adult patients have seen remarkable results from Revestive® when other treatments have failed. We think that it is important to offer this treatment to the more vulnerable pediatric population, who are at higher risks of long-term complications from early development of this disease, and who might never see improvement if they are unable to grow their bowel early on in the disease. Not everyone has responded to the current available treatments, so more options are essential. Short bowel syndrome patients have been suffering for too long from an inadequate variety of not very effective treatment options.

The parents of these small patients with short bowel syndrome want medications that help reduce symptoms so that their children can live their day-to-day lives more comfortably. In children, a focus on treatments that can help them develop a functional bowel and grow to a healthy weight and height for their age is especially important. Anything that can disconnect the child from TPN or EN feeding apparatuses is so valuable for physical and social development.

Hydrating digestive organs via intravenous means is not as efficient as getting fluids into the digestive system directly. Increasing oral consumption of water is vital for organ preservation, and with the use of Revestive®, these children can drink more than only a few drops of water.

5. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways?

This product is in clinical trial globally with 40 children, 3 of whom are in Canada. We were able to speak with the parent of one and the nurse practitioner who is caring for this child and the other 2 as part of the trial.

We spoke with the mother of one girl, currently four years old, who developed short bowel syndrome after contracting necrotizing enterocolitis (NEC), a devastating disease that generally affects the intestine of premature infants, although this girl was full term and breastfed, so her case is remarkable. The wall of the intestine is invaded by bacteria, which causes local infection and inflammation that can ultimately destroy the wall of the bowel (intestine). This disease consumed almost 90% of this girl's intestine shortly after birth. See photo to the right showing her as an infant with the feeding apparatuses needed.



When she was selected for the trial, she could not eat or hydrate via an oral route. She began Revestive® at approximately two years of age, in July 2017, and has seen such great success with the medication that her use of TPN has decreased dramatically and she has increased her oral hydration ability. However, during the washout period of the clinical trial, which occurred after about six months on the drug, she did seem to lose this benefit within 8-10 days, but she did regain it when back on the trial drug. To go from only being able to take a few drops of water orally to drinking small amounts is life changing for this young girl.

As she seems to be getting more benefit from oral solids, under a dietitian's care, she has been able to decrease her TPN consumption by 30% so that although she still is on TPN every day, she can have several hours disconnected from the TPN machine, which is incredibly important to this child and her family. She can also now consume small amounts of Pedialyte®.

She went from TPN 20 hours a day to 16 hours a day, allowing for some unencumbered play and socializing time. Within the last few weeks, this has been further reduced to 14 hours a day and her parents see great improvement in her. This family has an older sibling and the family's entire schedule is centred around the TPN and G-tube feeding of this little girl. The whole family is usually housebound or in hospital. She has a central line for TPN and another IV for hydration and the G-Tube for other nutrition. However, her appetite has increased and she can eat a wide variety of foods and is obtaining nutrition from real foods, so her G-tube feeding is also decreasing.

The mother stressed that this is an all-encompassing experience for the entire family. They can never sleep through the night. One or both parents must wake up three times during the night to check on equipment and monitor the daughter. This activity disturbs the entire household and is their new normal. From a financial standpoint, the girl's TPN and IV equipment and nourishment is covered but the ostomy supplies are not. Because of her high output, this is very costly. High use of TPN can lead to gallstones and liver damage to the point of needing transplant, so this child is still at risk of many consequences. Her parents are extremely grateful for the benefits to the family while being on the trial and notice a remarkable improvement in their daughter's health.

A boy in the trial has improved to the point that he can sleep for two nights a week unattached to any feeding apparatus, which greatly improves his restfulness.

This indication is essential for children who, without this effective medicine, will suffer life-long effects. When a child who has short bowel syndrome does not get this drug that can miraculously adapt their digestive tract early and regularly, they could face a very poor quality of life, often confined to hospitalization, with multiple organ failure, lack of normal socialization, failure to thrive, and even childhood death. We know this medication is expensive, but for these rare children who need help, it is greatly needed. The TPN treatment is also very expensive, and this could be reduced as the function of the intestine increases with the use of Revestive®. In children, it is especially important to ensure adequate treatment while growing, so that they can become healthy, well-adjusted, economically-contributing adults. We urge you to ensure that this Health Canada approved medication for pediatric short bowel syndrome patients who are on TPN is included with your list of positive recommendations for coverage.

6. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert



"Having short bowel syndrome has impacted every aspect of our daughter's life, and we are never free from the thought of the limitations this condition has placed on her future. Teduglutide has offered us a glimmer of hope. The improvement in her quality of life (and consequently on her sister and us as her caregivers) as a result of being on teduglutide has been remarkable."

~mother of this beautiful little girl



Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Shire Pharma Canada 2018	✓ \$5K			
Shire Pharma Canada 2017			✓ \$14K	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Gail Attara

Position: Chief Executive Officer

Patient Group: Gastrointestinal Society

Date: 2019-04-25