CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

TEDUGLUTIDE (REVESTIVE — SHIRE PHARMACEUTICALS IRELAND LIMITED)
Indication: treatment of adults and pediatric patients 1 year of age and above with Short Bowel Syndrome who are dependent on parenteral support

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that teduglutide should be reimbursed for the treatment of pediatric patients 1 year of age and above with short bowel syndrome who are dependent on parenteral support only if the following conditions are met:

Conditions for Reimbursement

Initiation criteria
1. Children between 1 and 17 years old.
2. Parenteral support requirements must be stable or there must have been no improvement in enteral feeding for at least the preceding three months.
3. Parenteral support must provide more than 30% of caloric and/or fluid/electrolyte needs.
4. The cumulative lifetime duration of parenteral support therapy must be at least 12 months.

Renewal criteria
1. Parenteral support volume and percentage of total consumption should be documented at each clinic visit.
2. Initial treatment response should be assessed 6 months after initiating treatment with teduglutide.
3. A positive response to treatment response is defined as at least a 20% reduction in parenteral support volume compared to the baseline volume.
4. Assessment for subsequent renewals should be carried out at 6 months intervals.

Discontinuation criteria
1. Discontinuation of treatment should be based on the prescribing physician's assessment of the patient's response and tolerance to treatment with teduglutide.

Prescribing conditions
1. Initiation and assessment for continued treatment though renewal of reimbursement of teduglutide should be done only by physicians currently working within a specialized multi-disciplinary intestinal rehabilitation program.

Pricing conditions
1. Reduced price.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	1.0
Publication Date:	November 2019
Report Length:	9 Pages

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Reasons for the Recommendation

1. Two phase 3 studies (Study 006, double-blind randomized study, N=59; and Study 003, an open-label non-randomized study, N=42) evaluated the efficacy and safety of teduglutide in pediatric patients (> one year of age) with SBS. In the two studies, teduglutide therapy 0.05 mg/kg for 24 weeks in Study 006 and 0.05 mg/kg for 12 weeks in Study 003, was compared to SOC. In Study 006, 69.2% (18 of 26) in the teduglutide 0.05 mg group and 11.1% (1 of 9) in the SOC group were responders (defined as patients who achieved ≥ 20% reduction in parenteral support (PS) volume at the end of treatment [EOT]) based on patient diary data. Treatment with teduglutide at a dose of 0.05 mg/kg was related to greater reduction in PS volume and infusion time from baseline to EOT compared to the SOC group. In Study 003, 53.3% (8 of 15) in the teduglutide 0.05 mg group and no patient (0 of 5) in the SOC group were responders; and teduglutide was related to greater reduction in PS volume and infusion time from baseline to Week 12 compared to the SOC group.

2. The addition of teduglutide to best supportive care (BSC) is not a cost-effective option at a cost-effectiveness threshold of $50,000 per quality-adjusted life-year (QALY). In CADTH's re-analysis, teduglutide plus BSC was associated with an incremental cost-utility ratio (ICUR) of $1,638,499 per QALY gained compared with BSC in pediatric patients with SBS. Furthermore, this estimate is associated with significant uncertainty due to limitations in the data and model structure. A price reduction of at least 71% would be required to achieve an ICUR below a willingness-to-pay (WTP) threshold of $50,000 per QALY.

Implementation Considerations

- Teduglutide was previously recommended for reimbursement by CDEC for adult patients. Drug plans should consider any existing reimbursement conditions, including pricing arrangements, when implementing reimbursement of teduglutide for children, while recognizing that certain reimbursement conditions are specific to pediatric patients.

Discussion Points

- CDEC noted the unmet need in the population of pediatric patients with SBS and recognize that the symptoms and complications of SBS compromise the quality of life of children and families. The committee noted that there is currently no medication available to stimulate intestinal differentiation and growth which could help eliminate the need for parenteral nutrition and result in an increase in the use of oral or enteral feeding.
- CDEC acknowledged that current intestinal rehabilitation programs in large Canadian centers continue to make progress in achieving enteral autonomy when managing pediatric patients with SBS.
- Teduglutide 0.05 mg/kg/day is the only Health Canada approved dosage.
- There continues to be substantial uncertainty on the impact of teduglutide on clinical outcomes due to the small sample sizes in the clinical trials. Likewise, the effect of treatment with teduglutide on long-term outcomes has not been established in comparative trials. CDEC recommends additional trials be conducted in the pediatric population, with similar methodology to those conducted in adult patients with this condition. CDEC heard clinical expert opinion that despite the small sample sizes in the trials, the inclusion and exclusion criteria used in the trials reflect pediatric patients with SBS in Canada.
- CDEC noted that the clinical benefits associated with a ≥ 20% reduction in parenteral support volume are unknown. However, the committee heard clinical expert opinion that this outcome is considered clinically meaningful by physicians specialising in the treatment of pediatric patients with SBS in Canada.
- CDEC noted that the clinical and patient characteristics that could predict response to teduglutide are unknown at this time and further studies are needed to determine who can benefit most from the drug. CDEC also heard clinical expert opinion that predicting the impact of teduglutide discontinuation in pediatric patients with SBS who adapted and were weaned off parenteral support is not yet known. Additional research is needed.

Background

Teduglutide has a Health Canada indication for treatment of adults and pediatric patients one year of age and above with short bowel syndrome (SBS) who are dependent on parenteral support. Teduglutide is an analog of naturally occurring human glucagon-like peptide-2. Teduglutide is available as powder for solution for injection, 5 mg/vial. The Health Canada–approved dose is 0.05 mg/kg body weight administered by subcutaneous injection once daily.

Submission History

Teduglutide was previously reviewed for the treatment of adults with SBS who are dependent on parenteral support. It received a recommendation of "be reimbursed for the treatment of short bowel syndrome", with the following conditions and criteria (see Notice of CDEC Final Recommendation, July 27, 2016):

Criteria:

- Therapy with teduglutide should be restricted to patients who meet the enrolment criteria of the clinical trials:
  - Age ≥18 years
  - SBS is a result of major intestinal resection (e.g., due to injury, volvulus, vascular disease, cancer, Crohn's Disease)
  - Resection resulting in dependency on parenteral nutrition (PN) for at least 12 months
  - PN required at least three times weekly to meet caloric, fluid or electrolyte needs due to ongoing malabsorption
  - PN frequency and volume have been stable for at least one month
- Therapy should be discontinued if a 20% reduction in PN volume has not been achieved within 24 weeks of teduglutide therapy.

Conditions:

- Substantially reduced price
- Therapy should be managed by a specialist with experience in SBS

Summary of Evidence Considered by CDEC Considerations

The committee considered the following information prepared by the Common Drug Review: a systematic review that included two clinical trials of teduglutide and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with SBS, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Gastrointestinal Society, provided input for this submission. Patient perspectives were obtained from interviews with healthcare professionals and parent of a patient who was involved in a Revestive pediatric trial, published information, conference, and expert opinion. The following is a summary of key input from the perspective of the patient group(s):

- SBS is a potentially fatal condition in which patients are unable to absorb sufficient nutrients and fluids through the intestines. Patient's physical, mental and social wellbeing are significantly affected.
- Current therapy for patients with SBS includes one or a combination of the following – dietary adjustments, parenteral support, enteral feeding and surgery. Each treatment is associated with different drawbacks.
- Two areas of unmet needs were identified for the pediatric patients: 1) a shortage of effective treatments for children who are at a higher risk of long-term complications from an early onset of SBS, and for children who are unable to grow bowel – therefore treatments that can help them develop a functional bowel is particularly important for their normal growth; and 2) a treatment option that can circumvent the need for parenteral support or enteral feeding apparatuses will be valuable for children to live their day-to-day lives more comfortably, allowing for a normal physical and social development.
- Feedback for teduglutide (provided by the parent of a child suffering from SBS) suggested great clinical benefits since starting the treatment, and consequently, the family of the child benefitted significantly as well as the associated financial benefits.

Clinical Trials

The systematic review included two clinical trials submitted by the manufacturer that evaluated the efficacy and safety of teduglutide in pediatric patients (> one year of age) with SBS. In both trials, the participants required parenteral support (PS) that provided at least 30% of caloric and/or fluid/electrolyte needs for at least 3 months prior to screening and was stable for more than 3 months prior to and during screening. In the two trials, teduglutide therapy (0.025 mg/kg and 0.05 mg/kg for 24 weeks in Study 006, N=59; 0.0125 mg/kg, 0.025 mg/kg and 0.05 mg/kg for 12 weeks in Study 003, N=42) was compared with standard of care (SOC). Patients and their caregivers decided whether they wanted to receive teduglutide or SOC. In Study 006, patients who selected the teduglutide therapy were randomized to 0.025 mg/kg or 0.05 mg/kg regimen. In Study 003, patients' dose of teduglutide was assigned based on when they enrolled in the study. Teduglutide 0.05 mg/kg/day is the only Health Canada approved dosage for the study population.

Key limitations of the reviewed trials are the study design and the lack of a statistical comparison between treatment groups. Patients were not randomized to receive teduglutide and comparator. Patients and their caregivers decided whether they wanted to receive treatment or SOC. Therefore, systematic differences in age, race, nutritional status, underlying causes for SBS and remaining small intestinal length were observed between treatment groups and have an impact on data interpretation. Statistical testing was not performed, and data were descriptively summarized only.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following: change in parenteral feeding (measured using proportion of patients with ≥ 20% reduction in PS volume or change from baseline in PS volume) and change in enteral feeding (measured using change from baseline in enteral nutrition [EN] volume or complete weaning off PS). In the trials, responders were defined as patients who achieved ≥ 20% reduction in PS volume from baseline to study endpoint, which was Week 24 in Study 006 and Week 12 in Study 003. Enteral autonomy was defined as complete weaning off PS at the end of study.

The primary outcome in Study 006 was the number of patients with ≥ 20% reduction in PS volume from baseline to Week 24. Study 003 did not specify the primary outcome, while the number of patients with ≥ 20% reduction in PS volume from baseline to Week 12 was reported along with other efficacy outcomes. The results were reported based on two data sources: patient diary data and the investigator-prescribed data.

Quality of life outcomes were not studied, although they were identified as important outcomes of interest to patients with SBS.

Efficacy

Change in parenteral feeding

In Study 006, 54.2% of patients in the teduglutide 0.025 mg group, 69.2% in the teduglutide 0.05 mg group and 11.1% in the SOC group were responders, based on patient diary data. Analysis of investigator-prescribed PS volumes gave consistent results, [redacted]. The experts consulted on this review considered these differences between treatment and SOC to be clinically meaningful; however, statistical comparisons were not performed. Treatment with both teduglutide doses was related to greater reduction in PS volume from baseline to Week 24 compared to the SOC group: percentage change in PS volume from baseline was -36.2%, -41.6% and -10.2% in the teduglutide 0.025 mg/kg, teduglutide 0.05 mg/kg and the SOC groups, respectively.

In Study 003, 12.5% of the patients in the teduglutide 0.0125 mg group, 71.4% in the teduglutide 0.025 mg group, 53.3% in the teduglutide 0.05 mg group and no patient in the SOC group achieved ≥ 20% reduction in PS volume at Week 12, based on patient diary data. [redacted]. The experts considered these differences between teduglutide and SOC to be clinically meaningful; however, statistical comparisons were not performed. All teduglutide dose groups except for the 0.0125mg/kg were related to greater reduction in PS volume from baseline to Week 12 compared with the SOC group: [redacted].

Change in enteral feeding

In Study 006, patients in both teduglutide groups experienced greater increase in EN volume from baseline to Week 24 compared to the SOC group (percentage change of 76.9%, 79.5% and 2.5% for teduglutide 0.025 mg/kg group, teduglutide 0.05 mg/kg group and the SOC group, respectively). Two patients (8.3%) in teduglutide 0.025 mg/kg group and three (11.5%) in the teduglutide 0.05 mg/kg group achieved enteral autonomy, while no patients from the SOC group achieved enteral autonomy.

In Study 003, all three teduglutide groups experienced greater increase in EN volume from baseline to Week 12 compared with the SOC group ([redacted]). In Study 003, one patient (7.1%) in the teduglutide 0.025 mg/kg group and three patients in the teduglutide 0.05 mg/kg (20.0%) achieved enteral autonomy at Week 12.

Harms (Safety)

Almost all patients reported treatment-emergent adverse events (AEs) in Studies 006 and 003. The majority of the AEs were mild or moderate in severity. The most common AEs reported in Study 006 by the pediatric patients treated with 0.05 mg/kg teduglutide were pyrexia (42%), cough (39%), vomiting (31%), upper respiratory tract infection (31%), abdominal pain (23%) and nasopharyngitis (23%). Although the proportion of patients with AEs was higher in the teduglutide groups for most of the reported AEs, the risk of certain AEs was higher in the SOC group, such as vomiting, pyrexia and upper respiratory tract infection.

In Study 006, the incidence of serious adverse events (SAEs) was higher in teduglutide-treated groups (63% to 77%) than in the SOC group (44%), while in Study 003, treatment with teduglutide 0.05 mg/kg (53.3%) or SOC (60.0%) was associated with more SAEs, as compared with teduglutide 0.0125 mg/kg (37.5%) or teduglutide 0.025 mg/kg (42.9%). Common SAEs in the included trials were pyrexia, dehydration and central line-related breakage or infection.

No patients withdrew due to AEs and no deaths were reported in either study. In terms of AEs of special interest, during the study, there were no report of gastrointestinal tract polyp formation, biliary complications, neoplasia or intestinal obstruction in either study. At the end of the study, antibody development was detected in eight patients in Study 006 (3 in the teduglutide 0.025 mg/kg group, 5 in the teduglutide 0.05 mg/kg group) and one patient (teduglutide 0.025 mg/kg group) in Study 003.

Cost and Cost-Effectiveness

Teduglutide is available as a 5 mg single-use vial for subcutaneous injection. The recommended dose is 0.05 mg per kilogram of body weight daily. At the sponsor's submitted price of $904 per vial, the annual cost of teduglutide in patients weighing up to 100 kg is $329,960 per patient.

The sponsor submitted a cost-utility analysis comparing teduglutide plus BSC with BSC alone in pediatric patients (aged 1 to 17 years) with SBS who are PS-dependent. BSC was defined as the provision of PS and oral medication to relieve symptoms, such as antisecretory agents, antimotility agents, and antibiotics. The analysis was conducted from the perspective of the Canadian publicly funded health care system over a lifetime time horizon (94 years). The manufacturer submitted a Markov state transition model in which patients could transition between four health states defined by intensity of parenteral nutrition required, or to an absorbing death state. Efficacy data for teduglutide and BSC were derived from Study 006 with stopping rules applied based on response (i.e., achieving PS independence) and non-response (i.e., not achieving 20% volume reduction in PS at 24 weeks). The model further included all serious AEs observed in Study 006. Health state utility values for patients were obtained from a vignette study while caregiver disutilities for PS dependent patients were derived from a manufacturer commissioned Delphi panel study and caregiver survey. In the sponsor's probabilistic base case analysis, teduglutide was associated with an ICUR of $713,887 per QALY gained compared to BSC alone and had a 0% probability of being a cost-effective intervention at willingness-to-pay-threshold of $50,000 per QALY.

CADTH identified several key limitations with the submitted analysis:

- Comparative efficacy was based on a non-randomized comparison between teduglutide and standard of care. It is unclear whether standard of care within Study 006 reflects current clinical practice (and BSC, as modelled in the economic analysis). The sponsor's assumption that pediatric patients can not improve with BSC after the trial-observed period also differs from clinical experts' experience with PS within this patient population.
- Model structure did not reflect all relevant impacts of the treatment and the condition. Mortality estimates were based on populations that are unlikely to be comparable to pediatric patients with SBS and the sponsor's model did not consider the potential costs and utility impacts of patients requiring enteral nutrition.
- Impact to caregiver (i.e., caregiver disutilities) should not be included in a public payer perspective.

- Treatment was assumed to be discontinued if a patient achieved PS independence, which is not consistent with clinical practice, as indicated by clinical experts. This assumption would likely underestimate the cost of teduglutide.
- Only AEs requiring complex treatment, as reported in Study 006, were included in the sponsor's base-case analysis rather than incorporating the AEs that were considered clinically meaningful.

CADTH re-analysis accounted for some of the identified limitations by: removing caregiver disutilities; assuming that treatment continued even after a patient achieved PS independence; and, incorporating serious AEs that were identified as being clinically meaningful by clinical experts consulted by CADTH. The ICUR for teduglutide plus BSC was $1,638,499 per QALY gained compared with BSC alone in pediatric patients with SBS. CADTH was unable to address most key limitations including uncertainties associated with the model structure, the clinical efficacy of teduglutide plus BSC compared to BSC, and the predictions on long-term mortality. As such, the results of this economic evaluation should be viewed with caution.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

October 16, 2019 Meeting

Regrets

2 CDEC member(s) did not attend.

Conflicts of Interest

None