



CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

Teduglutide

(Revestive – Shire Pharma Canada ULC/ NPS Pharma Holdings Ltd.)

Indication: For the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that teduglutide be reimbursed for the treatment of short bowel syndrome (SBS), with the following conditions and criteria:

Criteria:

- Therapy with teduglutide should be restricted to patients who meet the enrolment criteria of the clinical trials:
 - Age \geq 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 parenteral nutrition 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.

Reasons for the Recommendation:

1. Two double-blind, placebo-controlled, randomized trials (CL04 and CL20) found that teduglutide 0.05 mg/kg/day was associated with better graded response scores than placebo. CL20 showed that teduglutide 0.05 mg/kg/day was associated with statistically significant higher reduction in PN volume than placebo. CL20 also showed that teduglutide was associated with a reduction in the number of PN days/week.
2. Based on a CDR analysis, the incremental-cost utility ratio (ICUR) for teduglutide ranges between \$1,588,364 and \$1,666,666 per QALY compared with the current standard of

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care, suggesting that at its current price without substantial restrictions of at least 80%, it represents very low value.

Research gaps:

CDEC noted the following research gaps exist for drug treatment in SBS:

- There continues to be substantial uncertainty on the impact of teduglutide on clinical outcomes due to the small sample sizes in the study, the exploratory nature of CL04 and the inconsistent results between CL04 and CL20.
- The effect of drug treatment on long-term outcomes has not been established in comparative trials.

Background:

Teduglutide has a Health Canada indication for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral nutrition. Teduglutide is a 33-amino acid recombinant analog of human GLP-2, a peptide secreted primarily from the lower gastrointestinal tract. It is available as 5 mg vials for subcutaneous injection and the Health Canada approved dose is 0.05 mg/kg/day.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review: a systematic review of pivotal and published phase III trials of teduglutide, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information:

- One patient group, the GI (Gastrointestinal) Society, provided patient input.
- Patient experiences can vary. Common symptoms include vitamin and mineral deficiencies, frequent diarrhea, extreme fatigue, cramping, dehydration, and weight loss. Complications of these can include peptic ulcer disease, kidney stones, gallstones, small bowel bacterial overgrowth, and metabolic bone disease. Because so much of family and social life involves food, patients often miss out on important occasions and become more isolated.
- Caregivers need to devote physical, emotional, and financial resources to a family member with short bowel syndrome. They might need to take time off work to assist with preparing and administering feeding and with other tasks. These can include cooking, cleaning, errands, physical hygiene care, and transporting the patient to medical appointments. These demands can result in financial hardship, stress, and anxiety. Relationships can become strained, which sometimes leads to struggles within the family.
- The patient group reported that patients who undertook treatment with teduglutide had more energy, less fatigue, and a general increase in their quality of life. Patients also reported that they were able to eat and thus were less dependent on PN and had less diarrhea and more regular bowel movements.

Clinical Trials

The systematic review included two double-blind, randomized, placebo-controlled trials of patients with short bowel syndrome (CL04 and CL20).

The objective of the included studies was to evaluate the efficacy, safety, and tolerability of teduglutide compared with placebo in patients with PN-dependent SBS. In CL04, 84 patients

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were randomized in a 1:2:2 ratio to one of three treatment arms: placebo, 0.05 mg/kg/day teduglutide, or 0.10 mg/kg/day teduglutide. In CL20, 86 patients were randomized in a 1:1 ratio to one of two treatment groups: 0.05 mg/kg/day teduglutide or placebo.

“Graded response score” was the primary outcome in CL04, and a secondary outcome in CL20. It is a scoring algorithm that takes both response intensity (20 to 100% reduction in PN volume from baseline) and duration between weeks 16 and 24 into account. The primary efficacy variable in CL20 was the percentage of patients who demonstrated a response (20 to 100% reduction from baseline in weekly PN/I.V.) at Week 20, and who maintained that response at Week 24 (responder). In CL04, Health Related Quality of Life (HRQoL) was evaluated using SF36, EQ5D, and Inflammatory Bowel Disease Questionnaire (IBDQ); none of these measures had a specific MCID for patients with short bowel syndrome. In CL20, QoL was evaluated using a disease-specific measure called Short Bowel Syndrome QoL (SBS-QoL) questionnaire. The manufacturer defined the MCID for SBS-QoL as a positive change of the subjects’ QoL from Baseline above the twofold measurement error of the SBS-QoL (i.e. 18.4).

The two studies had selective inclusion criteria and excluded many diseases that may result in SBS including radiation enteritis, scleroderma, and celiac disease. This limits the generalizability of the study findings. Other limitations in the reviewed trials include the relatively small sample size, short double-blind treatment duration, and presence of some imbalance in baseline characteristics. Furthermore, study CL04 had a major deviation from the statistical analysis plan that affects the interpretation of findings.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: survival, parenteral feeding and fluid requirements, quality of life, and healthcare resource utilization. The primary outcome in the two trials was related to parenteral feeding and fluid requirements.

Efficacy

- There were no deaths reported in the included studies.
- Both trials showed that teduglutide 0.05 mg/kg/day was associated with better graded response scores than placebo, and two patients in CL04 were reported to be weaned from parenteral nutrition.
- Results from CL04 should be interpreted as exploratory because it failed to show statistical difference between 0.10 mg dose and placebo, which was the first step in their hierarchical testing procedure, and the 0.05 mg dose was not to be tested if this first step in the testing hierarchy failed.
- CL04 showed that neither teduglutide dose was statistically different from placebo in reducing the weekly parenteral nutrition volume.
- CL20 showed that teduglutide 0.05 mg/kg/day was associated with statistically significant higher reduction in PN volume than placebo.
- CL04 showed that the overall results from three quality of life (QOL) assessments (SF-36, EuroQoL EQ-5D and IBDQ) indicated no major effect on HRQoL parameters.
- CL20 did not show statistically significant HRQoL differences between the teduglutide and the placebo group after 24 weeks treatment as measured with SBS-QoL

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- CL04 showed that by the end of 24 weeks of treatment, teduglutide 0.05 mg/kg/day group had a higher rate of hospitalization than placebo (17% vs. 6%), but a lower rate of outpatient medical care (31% vs. 50%). There was no statistical testing of these differences.

Harms (Safety and Tolerability)

- The number of patients with adverse events, serious adverse events, or discontinuations due to treatment emergent serious adverse events was comparable between treatment groups.
- The most frequently reported treatment emergent adverse events in the teduglutide group were of gastrointestinal origin, such as abdominal pain, nausea, gastrointestinal stoma complication, or abdominal distension.
- There were no major findings reported in the laboratory/chemistry or hematology tests of the teduglutide-treated vs. placebo patients.

Cost and Cost-Effectiveness

At the submitted confidential price of ██████ per 5 mg vial, the daily dose of teduglutide (0.05 mg/kg) is ██████ per patient weighing 100 kg or less (or ██████ annually).

The manufacturer submitted a cost-utility analysis comparing teduglutide to standard of care (SOC) in adult patients with SBS who are parenteral support (PS)-dependent. Standard of care consisted of sufficient volume of parenteral nutrition or support and management of symptoms, if required. Efficacy data for teduglutide and SOC were derived from the STEPS trials. The utility inputs for the PS health states were from a Canadian study conducted by the manufacturer via a web-based survey for the general population. The analysis was conducted from the perspective of a Canadian publicly-funded health care system with a 40-year time horizon. The manufacturer reported an incremental cost-utility ratio (ICUR) for teduglutide compared to SOC of \$1,600,145 per quality-adjusted life-year (QALY) gained.

CDR identified the following key limitations with the manufacturer's economic submission:

- The stopping rule for patients receiving teduglutide, who do not experience at least a 20% reduction in PS after 24 weeks of treatment, was not applied in the economic evaluation. In the teduglutide clinical trials, patients who did not experience at least a 20% reduction in PS at 24 weeks were not permitted to continue treatment. This was confirmed as appropriate by the CDR Clinical Expert. CDR noted that where this stopping rule is applied the cost-effectiveness results for teduglutide will improve.
- The health state utilities used in the model were from a web-based unpublished survey of panelists from the Canadian general population conducted by the manufacturer, for which there exists some uncertainty in the values.
- The disutility associated with intestinal failure-related liver disease was derived from a study that reported utility scores for chronic liver disease in the United Kingdom population and was not specific to PS-related liver diseases; the generalisation of this data to the current context is questionable.

Despite the correction of identified limitations, the results were not sensitive to these changes, with the ICUR remaining between \$1,588,364 and \$1,666,666 per QALY for teduglutide compared with SOC. The high ICUR is driven by the high cost of treatment with teduglutide, the continued need for parenteral nutrition/support, and inconsistent clinical effects observed in

the trials (CL04 and CL20). Based on the manufacturer's base case, a price reduction of 80% would be required to achieve an ICUR of ~\$100,000 per QALY for teduglutide compared with SOC.

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, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeyesundera.

April 20, 2016 Meeting

Regrets: None.

Conflicts of Interest: None.

July 20, 2016 Meeting:

Regrets: None.

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. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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CDEC Meeting – April 20, 2016, CDEC Reconsideration July 20, 2016

Notice of Final Recommendation – July 27, 2016

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