CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

TEDUGLUTIDE (REVESTIVE)

(Shire Pharmaceuticals Ireland Limited)

Indication: Treatment of adults and pediatric patients one year of age and above with short bowel syndrome who are dependent on parenteral support.

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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Table of Contents

Tables

Figures

Abbreviations

AE	adverse event
BSC	best supportive care
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
EA	enteral autonomy
EN	enteral nutrition
GI	gastrointestinal tract
ICUR	incremental cost-utility ratio
IFALD	intestinal failure-associated liver disease
ITx	intestinal transplantation
HRQoL	health-related quality of life
QALY	quality-adjusted life-year
OS	overall survival
PN	parenteral nutrition
PS	parenteral support
RCT	randomized controlled trial
SBS	short bowel syndrome
SOC	standard of care
WTP	willingness-to-pay

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Teduglutide (Revestive)
Study Question	From the perspective of the publicly funded health care payer in Canada, what is the incremental cost-effectiveness of teduglutide with BSC compared with BSC alone in pediatric patients with SBS, aged 1 to 17 years?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Canadian pediatric patients with SBS, aged 1 year to 17 years, who are dependent on PS
Treatment	Teduglutide, 0.05 mg per kilogram injected subcutaneously once daily, along with BSC
Outcome	QALY
Comparator	BSC, consisting of symptom-relieving oral medication and PS as required
Perspective	Canadian publicly funded health care payer
Time Horizon	Lifetime horizon (up to 94 years)
Results for Base Case	ICUR = $713,887 per QALY gained
Key Limitations	CADTH identified several key limitations with the submitted analysis: • Comparative efficacy was based on a non-randomized comparison between teduglutide and SOC. It is further unclear whether SOC within the clinical trial reflects current clinical practice (and BSC). The manufacturer's assumption that pediatric patients cannot improve with BSC after the trial-observed period also differs from clinical experts' experience with PS within this patient population. • Mortality estimates were based on populations that are unlikely to be comparable to pediatric patients with SBS and given the paucity of available data, uncertainty around the target population's mortality remains. • The manufacturer's model did not accurately capture the condition as it 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 serious AEs reported within the trial were included in the model; thereby, omitting AEs considered clinically meaningful to clinical experts who were consulted by CADTH.
CDR Estimate(s)	The CADTH base-case reanalysis removed the treatment stopping rule due to PS independence, removed caregiver disutilities, and included only the most relevant serious AEs as identified by clinical experts consulted by CADTH. • Based on these revisions, the ICUR of teduglutide with BSC compared with BSC alone was $1,638,499 per QALY gained. • A price reduction of at least 71% would be required for teduglutide to be considered cost-effective at a $50,000 per QALY threshold. • CADTH was unable to address most key limitations including uncertainties associated with the model structure, the clinical efficacy of teduglutide plus BSC compared with BSC, and the predictions on long-term mortality.

AE = adverse event; BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PS = parenteral support; SBS = short bowel syndrome; SOC = standard of care.

Drug	Teduglutide (Revestive)
Indication	Treatment of adults and pediatric patients 1 year of age and above with short bowel syndrome (SBS) who are dependent on parenteral support
Reimbursement request	Treatment of adults and pediatric patients 1 year of age and above with SBS who are dependent on parenteral support
Dosage form(s) and route of administration)/strength(s)	Powder for solution, 5 mg/vial, subcutaneous injection
NOC date	August 13, 2019
Manufacturer	Shire Pharmaceuticals Irelands Limited

Executive Summary

Background

Teduglutide (Revestive) is indicated for use in adult and pediatric patients (one year of age and above) with short bowel syndrome (SBS) who are dependent on parenteral support (PS).[1] Teduglutide is available as a 5 mg single-use vial, for subcutaneous injection by a nurse, caregiver, or by self-administration. Optimization and stabilization of intravenous fluid and nutritional support should be performed before initiation of treatment.[1] At the manufacturer's submitted price of $904.00 per vial[2] and at a recommended dose of 0.05 mg/kg of body weight once daily as per the Health Canada–approved product monograph,[1] the annual cost of teduglutide in patients weighing up to 100 kg is $329,960.

Teduglutide was previously reviewed by CADTH in 2016 for the treatment of adult patients with SBS who are dependent on PS. The CADTH Canadian Drug Expert Committee (CDEC) recommended listing teduglutide with clinical criteria as follows: patients greater or equal to the age of 18 whose SBS resulted from major intestinal resection, who have been dependent on parental nutrition (PN) for at least 12 months, who require PN at least three times per week, and who have had a stable PN frequency and volume for at least one month. Treatment should be discontinued if a 20% reduction in PN volume has not been achieved within 24 weeks.[3] The manufacturer's submitted price for teduglutide at the time of this CADTH Common Drug Review (CDR) submission (pediatric population) was identical to the submitted price in the previous submission (adult population), at$904 per vial.[3] The manufacturer is presently requesting reimbursement for the pediatric indication.[2]

The manufacturer submitted a cost-utility analysis comparing teduglutide plus best supportive care (BSC) with BSC alone in pediatric patients 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.[2] The analysis was conducted from the perspective of the Canadian publicly funded health care system over a lifetime time horizon (94 years) with cycles defined as every 28 days. Future costs and benefits were discounted at 1.5%.[2] The model structure consisted of a Markov state transition model in which patients can transition between four unique health states defined by intensity of parenteral nutrition required or to an absorbing death state.[2] Efficacy data for teduglutide and BSC were derived from one clinical trial (Study 006).[2] Stopping rules based on response (achieving PS independence) and non-response (not achieving 20% volume reduction in PS at 24 weeks) were incorporated into the manufacturer's model. The model

further included PS state-specific rates of developing intestinal failure-associated liver disease (IFALD) with inputs informed by a clinical Delphi panel that provided adult estimates, and all serious adverse events (AEs) observed in Study 006.[2] Mortality of SBS patients over the modelled time horizon was estimated using data from Fullerton et al.[4] Health state utility values for patients were obtained from a vignette study. Caregiver disutilities for PS-dependent patients were derived from a manufacturer's commissioned Delphi panel study and caregiver survey.[2] Disutilities for AEs were informed by published literature.[5,6] Costs reflected Canadian sources and included the costs of teduglutide, home PS, and AE management costs.[7,8]

The manufacturer reported that teduglutide with BSC is associated with an incremental cost-utility ratio (ICUR) of $713,887 per QALY gained compared with BSC alone.[2] Teduglutide had a 0% probability of being a cost-effective intervention at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained.

Summary of Identified Limitations and Key Results

CDR identified several limitations with the submitted economic analysis.

The evidence on comparative clinical efficacy for teduglutide is limited. With respect to Study 006, there was randomization of the two doses of teduglutide only, but no randomization performed on patients receiving standard of care (SOC).[9] Furthermore, it is unclear whether permitted treatments for patients receiving SOC – which informs the BSC comparator within the economic model – reflect current clinical practice, as it was insufficiently described. In extrapolating beyond the trial period, the manufacturer assumed that pediatric patients would not experience a reduction in PN needs with BSC; this does not align with the clinical experts' experience with PS. Specifically, pediatric patients may achieve PS independence due to bowel growth and intestinal adaptation,[2] and the manufacturer's assumption would favour teduglutide. There is limited evidence on the long-term survival of pediatric patients with SBS. According to the clinical experts consulted by CADTH, the data sources and assumptions applied by the manufacturer within their model do not appropriately reflect the target population.

The manufacturer's model structure was based on the intensity of PN[2] and did not consider that patients who achieve PS independence may still be dependent on enteral nutrition (EN), which has both costs and quality of life effects. The inclusion of caregiver disutilities is inappropriate under a public health care payer perspective. Clinical experts consulted by CADTH further questioned applying a stopping rule based on response, defined as achieving PS independence. Patients who achieve PS independence may continue to receive teduglutide if they are dependent on EN.[2] Even in patients who achieved enteral autonomy, the clinical experts noted that they may stop teduglutide but would require reassessment given concerns of rebound effects noted with this treatment in the adult population. By applying this stopping rule for response, this would favour teduglutide by underestimating treatment costs.

Other limitations included the cost of PS, the selection of AEs in the model, and the arbitrary definitions of uncertainty. The manufacturer conservatively estimated PS costs, which were reflected by the costs of providing PS in a home setting.[2,10] Clinical experts consulted by CADTH indicated that the cost of providing PN in a hospital setting is greater than the cost of home PS. Additionally, all serious AEs observed in Study 006 were captured in the manufacturer's model and this omitted some clinically meaningful AEs (e.g., central line infections) that were noted to be relevant by clinical experts consulted by CADTH. Lastly,

there were technical errors including applying an arbitrary definition to define uncertainty (20% of mean input estimates). The cost-effectiveness results of the submitted model may therefore not reflect the true uncertainty that would be associated with the model input parameters.

The CADTH revised base case addressed some of the identified limitations by assuming patients continue treatment even after achieving PS independence, incorporating serious AEs that were identified as being clinically meaningful by clinical experts consulted by CADTH, and removing caregiver disutilities. CADTH's base case resulted in incremental costs of $5,951,304 and incremental QALYs of 3.63 for teduglutide plus BSC compared with BSC alone, resulting in an ICUR of $1,638,499 per QALY gained. As it is uncertain when patients may stop treatment due to response, CADTH further conducted a scenario analysis that incorporated the manufacturer's stopping rule, which resulted in an ICUR of $1,106,536 per QALY gained.

Conclusions

A number of key limitations identified in the manufacturer's model had a large impact on the cost-effectiveness of teduglutide with BSC. CADTH's findings remained aligned with the manufacturer's: the addition of teduglutide to BSC is not a cost-effective option at a cost-effectiveness threshold of $50,000 per QALY. In CADTH's base case, teduglutide plus BSC was associated with an ICUR of $1,638,499 per QALY gained compared with BSC in pediatric patients with SBS. A price reduction of 71% would be required to achieve an ICUR below a WTP threshold of $50,000 per QALY. However, depending on the stopping rule, the ICUR may reduce to $1,106,536 per QALY gained if patients were assumed to never return to treatment after achieving their initial response.

Considerable uncertainty remains on the treatment effects of teduglutide plus BSC compared with BSC alone and the expected natural history of pediatric patients with this condition. The economic model was overall informed by a less robust clinical evidence base for the pediatric population than previously reviewed by CADTH. Limited natural history data resulted in a heavy reliance on assumptions, and limitations to the clinical trial design included small sample sizes, non-randomized comparisons, significant between-group heterogeneity, and short follow-up periods. All these could not be addressed by CADTH and interpretation of the economic results therefore warrants careful consideration.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing the initiation of teduglutide plus best supportive care (BSC) with BSC alone in pediatric short bowel syndrome (SBS) patients who are dependent on parenteral support (PS).[2] BSC was assumed to consist of PS and symptom-relieving oral medication such as antisecretory agents, antimotility agents, and antibiotics. The manufacturer adopted a lifetime time horizon from the perspective of the publicly funded health care payer.[2] Costs and clinical outcomes (i.e., quality-adjusted life-years [QALYs]) were discounted at a rate of 1.5% per annum with a half-cycle correction applied.[2] The model reflected a population that had similar baseline characteristics to Study 006 (mean age 6.2 years; 66.7% males).

The economic analysis was conducted using a Markov state transition model with cycle length defined as 28 days. The model included four PS health states (i.e., PS0, Low PS, Mid PS, High PS) and death (i.e., the absorbing health state).[2] The PS health states reflected the intensity of parenteral nutrition required (i.e., number of days per week a patient would be dependent on PS):

- PS0 = independent of PS (i.e., requires no PS)
- Low PS = requires 1 to 3 days of PS per week
- Mid PS = requires 4 to 5 days of PS per week
- High PS = requires 6 to 7 days of PS per week

At the start of the model, patients were distributed across the various PS health states according to the pooled baseline distribution for the intervention (teduglutide 0.05 mg/kg/d) and placebo arms, as observed in Study 006.[9] Patients could transition from their PS health state to any other PS health states, remain in their existing PS state, or die.[2] Transition probabilities in the economic model were estimated from Study 006.[2] For the trial period (24 weeks), time-dependent transition probabilities were calculated for both the treatment and comparator arms for every 28-day period. Specifically, as no changes were observed in PS state during the trial period for patients on placebo, it was assumed within the model that patients on BSC would remain in their baseline PS states.[2] In the extrapolation period, transition probabilities for teduglutide were derived under the assumption that the average probability of transitioning between PS health states between weeks 12 and 24 (i.e., last three months of the trial) would reflect the effect of teduglutide until the end of the second year of treatment. For the placebo arm, the manufacturer's model continued to assume that patients would remain in their baseline PS health states.[2] The manufacturer applied stopping rules, based on both a response and a non-response criteria. Patients were assumed to stop teduglutide if PS independence was achieved (i.e., "PS0" health state) or if a 20% volume reduction in PS was not achieved at 24 weeks of treatment, respectively. In patients who discontinued due to non-response, they were assumed to continue with BSC only and their transition probabilities reflected those in the BSC arm.[2]

The manufacturer incorporated all serious AEs observed within Study 006 as well as PS health state–specific rates of developing intestinal failure-associated liver disease (IFALD) according to published literature.[2] Background mortality was taken from age- and gender-

specific Canadian mortality tables.[2] Increased mortality risks for SBS and IFALD were applied to this background mortality. Specifically, the hazard ratio for death in PS-independent compared with PS-dependent patients was estimated from a study by Fullerton et al.[4] It was assumed that individuals achieving PS independence would have similar mortality rates to those of an age and gender-matched general population whereas the mortality of those dependent on PS was derived by applying the hazard ratio on the general population mortality to generate parametric survival curves.[2]

Utility values for each PS state, by patient, were based on a vignette study conducted in the UK to estimate health-related quality of life (HRQoL) values.[2,11,12] The manufacturer assumed 1.5 caregivers would be impacted until patients reached 18 years of age; thereafter, 0.8 caregivers would be impacted.[2] Caregivers of PS-independent patients would have a utility value equal to their age-adjusted general population values, while for PS-dependent patients, the model applied a PS state–specific utility decrement that was based on the manufacturer's commissioned Delphi panel study and caregiver survey. Adverse event disutilities were based on values from the literature.[5,6]

The cost of teduglutide was based on the manufacturer's submitted price and assumed no vial sharing (i.e., wastage of partially used vials).[2] A one-time initial cost of nurse-led training was assumed.[2] Furthermore, the manufacturer assumed that teduglutide would not result in differences in the use of symptom-relief medication given that medication for symptom relief would not address the underlying disease mechanism. The manufacturer assumed that PS state costs would be identical for pediatric and adult patients and applied a cost of home PS based on the literature.[10] Only adverse events (AEs) that required health care resources (e.g., hospitalization) were costed based on the OCCI case-costing tool.[8] All costs were reported in 2019 Canadian dollars.

Manufacturer's Base Case

Based on the manufacturer's probabilistic analysis, teduglutide plus BSC was associated with an additional cost of $4,099,348 and a gain of 5.75 additional QALYs compared with BSC. The resulting ICUR was $713,887 per QALY gained when compared with BSC (Table 2).

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of Teduglutide + BSC ($)	Total QALYs	Incremental QALYs of Teduglutide + BSC	Incremental Cost per QALY (ICUR)
BSC	$11,288,908	–	35.70	–	–
Teduglutide + BSC	$15,388,255	$4,099,348	41.45	5.75	$713,887

BSC = best supportive care; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted several deterministic one-way sensitivity analyses to address parameter uncertainty and probabilistic scenario analyses to test alternative assumptions. The results of the manufacturer's sensitivity analyses indicated that the model results were most sensitive to the transition probabilities for teduglutide between month two to month three.

The uncertainty around most input parameters in the manufacturer's model was assumed to be 20% of the parameter point estimate (e.g., mean value). The uncertainty observed in the results of the probabilistic base-case and scenario analyses may therefore not fully reflect the uncertainty around model parameters.

Limitations of Manufacturer's Submission

CADTH identified the following limitations with the manufacturer's model:

- **Uncertain comparative clinical evidence:** The economic model submitted by the manufacturer was based on Study 006 which only carried out randomization between the low and high dose teduglutide groups rather than between the teduglutide and standard of care (SOC) groups.[9] This study involved a small sample in which significant heterogeneity was detected between groups. The CADTH clinical review noted that Study 006 made a concerted effort to standardize SOC across various settings; however, as there are no current evidence-based clinical practice guidelines, there is the possibility that SOC may diverge from BSC in certain Canadian institutions.

  Although long-term extension studies are ongoing, patients received treatment on an as-needed basis.[9,13] The long-term comparative efficacy of teduglutide with BSC compared with BSC alone is therefore unknown and the cost-effectiveness results based on Study 006 should be interpreted with caution. The submitted model assumed that patients receiving BSC alone would remain in the same PS health state as baseline for the remainder of their lifetime. However, the clinical experts contacted by CADTH noted that this would only be an appropriate assumption if a patient had stopped growing (i.e., approximately between ages 5 years to 8 years). Prior to that age, the small bowel is expected to exhibit potential adaptive growth which suggests that a patient's condition may improve, provided that the small intestinal growth rate has not reached a plateau. The clinical experts consulted for this review indicated that with the current SOC, approximately 50% to 80% of children with SBS may achieve enteral autonomy. Given that the average baseline age within the model was 6.2 years, it is therefore an unreasonable assumption that no patients would naturally improve over time. However, given the paucity of natural history data, CADTH was unable to address this limitation. This is likely to underestimate the ICUR as patients who improve on BSC would have lower costs and improved QALYs.

- **Model structure does not reflect all relevant impacts of treatment and the condition:** Clinical experts consulted by CADTH noted that the health states defined within the manufacturer's model were misclassified and did not adequately capture the intended treatment goals. As noted in the CADTH clinical review, the most important treatment goals are to improve survival, to achieve enteral autonomy, to reduce dependency from PN/IV support while maintaining optimal nutritional status and health, and to minimize the complications associated with the disease and treatments in children with SBS. Of particular concern, the model only captured PS independence (i.e., patients who have completely weaned off PS at the end of the 24-week treatment), and this was the definition adopted in the clinical trials to define enteral autonomy. Clinical experts noted that even if patients achieve PS independence, they may be reliant on EN which has both cost and utility impacts. As health states were defined solely by the intensity of parenteral nutrition, the manufacturer's model is unable to capture the potential cost and utility impacts of patients with other nutritional needs. According to the clinical experts consulted by CADTH, a more appropriate categorization would be:
  - None (i.e., no medical intervention) = no PS required

- Low = no PS but other nutritional management required (e.g., enteral support)
- Moderate = requires 1 day to 3 days of PS per week
- High = requires 4 days to 5 days of PS per week
- Critical = requires 6 days to 7 days of PS per week

- **Mortality is highly uncertain:** In the two randomized trials submitted to CDR by the manufacturer, no deaths were reported. Therefore, to model the potential long-term impacts of treatment on mortality, the manufacturer had to model mortality based on published literature and assumptions. The manufacturer applied several clinically implausible assumptions regarding the mortality of the target population. First, the manufacturer's model assumed that SBS pediatric patients who achieved PS independence would have the same overall survival (OS) as age- and gender-matched general population.[2,14] Clinical experts consulted by CADTH noted that, even patients within the target population who achieve PS independence, would likely have a lower OS than their age- and gender-matched counterparts.

  Mortality was calculated for patients dependent on PS based on a study by Fullerton et al.[4] that reported an increased risk of mortality compared with patients who were PS independent. The clinical experts indicated that the Fullerton et al.[4] study was not reflective of the target population because the study included patients with other underlying causes of pediatric intestinal failure rather than patients with intestinal failure due to SBS. The effect of teduglutide on the long-term survival of the target population is unknown given the paucity of data and consideration of other critical factors affecting the mortality of pediatric patients with SBS. CADTH was unable to address this limitation but conducted scenario analyses by examining the impact of alternate parametric survival curves to explore the potential sensitivity of the model on mortality.
- **PS health state costs are underestimated:** The manufacturer incorporated the annual cost of home parenteral nutrition (PN) ($320,369), based on a study by Kosar et al.[10] According to clinical experts consulted by CADTH, the costs of in-hospital PS exceed the costs of home parental nutrition. Furthermore, the care required may be highly dependent on symptoms and availability of centres; and patients may need to go to highly specialized centres (e.g., the GIFT program at Sick Kids Hospital in Toronto for Ontario patients) which may further increase the costs of providing PS. Additionally, the cost calculated by Kosar et al.[10] does not include any training costs that would be required before a patient can receive PS at home. According to the clinical experts consulted by CADTH, PS training is crucial to educate patients on how to avoid central line complications such as infection. As existing costing analyses on PS are outdated and reflective of non-Canadian health care systems,[15,16] CADTH could not address this limitation but notes that the use of the manufacturer's values are likely to produce a more conservative estimate.
- **Caregiver impacts incorporated into the base case not appropriate for the public payer perspective:** The inclusion of utility impacts on caregivers was applied within the manufacturer's base case to all patients in all PS health states for the entirety of a patient's lifetime. The inclusion of caregiver utility values would not be applicable within the public payer perspective. According to CADTH guidelines,[17] all included costs and health effects should be directly related to the public payer perspective. Inclusion of caregiver disutilities would favour teduglutide, as patients on teduglutide required fewer days of PS each week.
- **Stopping rule for treatment response:** In the manufacturer's model, two stopping rules were applied based on criterion for response and non-response.[2] According to the clinical experts consulted by CADTH, the stopping rule for non-response was appropriate.

However, they would be reluctant to apply a stopping rule for response as defined by the manufacturer (i.e., patients who achieved PS independence at any time). The clinical experts noted that treatment discontinuation may be considered if patients achieve independence of EN. The proportion of patients who achieve this outcome within the trials is, however, not reported. As noted in the CADTH clinical review, the majority of children may respond to the drug, but few will achieve enteral autonomy. Another challenge with applying a stopping rule based on response was concerns of the risk of rebounding noted by the clinical experts given their experiences prescribing teduglutide in adults. This has not been considered in the submitted model. According to the clinical experts consulted, adult patients have exhibited a rebound effect when teduglutide is stopped, resulting in the need for treatment to be reinitiated (i.e., patients requiring either PS or PS plus teduglutide). As noted in the CADTH clinical review, there is a lack of data regarding the rebound of the condition and younger children may have a different experience and greater potential to wean off PN/IV, compared with adults. However, within Study 304 (extension study), among the seven patients who achieved enteral autonomy at the end of the first treatment cycle during the extension period, one patient required re-initiation with both PS and teduglutide during the subsequent treatment cycle in the extension period. The clinical experts consulted by CADTH noted that patients should be able to resume treatment with teduglutide after stopping due to response, if required (for example, due to deterioration in health state). While CADTH was unable to address the effects of discontinuation or rebound on the estimated costs and outcomes given the lack of available data, CADTH conservatively assessed the impact of this limitation by changing the stopping rule for response from “achieving PS independence at any time” to “no stopping rule.”

- **Selection of adverse events in the model:** The manufacturer’s base case incorporated all serious AEs (i.e., AEs requiring complex treatment, such as hospitalization). However, some clinically meaningful AEs (e.g., central line infection) noted by the clinical experts that were consulted by CADTH were not incorporated in the manufacturer’s model even if they met the above requirements. As per the CADTH guidelines, researchers should focus on harms that are clinically meaningful.[17]
- **Use of an arbitrary definition of uncertainty within the probabilistic sensitivity analysis:** The manufacturer applied an arbitrary definition of uncertainty in the probabilistic sensitivity analysis (i.e., the standard error of the mean was estimated to be 20% of the mean value for parameters) for most parameters in the model.[2] No appropriate justifications have been provided for this assumption. This approach in defining probability distributions is inappropriate as parameters with low sensitivity but higher uncertainty should impact the model’s output more than parameters with high sensitivity but estimated with greater precision. The uncertainty observed in the probabilistic results may therefore not fully reflect the true uncertainty around model parameters. CADTH did not address the impact of uncertainty on the estimated costs and outcomes.

CADTH Common Drug Review Reanalyses

CADTH conducted reanalyses to address some of the limitations listed above, which included:

1. Removal of a teduglutide stopping rule for response. This reflects a more conservative assumption than assumed by the manufacturer, given uncertainty due to the proportion of pediatric patients who achieve independence from enteral feeding and concerns by

the clinical experts consulted by CADTH that they may re-initiate patients with teduglutide upon discontinuation of treatment, if rebounding effects are observed.

2. Consideration of only clinically meaningful AEs, determined based on consultation with the clinical experts (i.e., pyrexia, dehydration, catheter site erythema, catheter site infection, catheter site related reaction, and injection site rash)
3. Removal of caregiver disutilities to reflect the perspective of the publicly funded health care payer.

Results of the reanalyses are presented in Table 3. The removal of caregiver disutilities impacted the model results the most as it led to a substantial reduction in total QALYs. The CADTH base case combined all reanalyses resulting in an ICUR of $1,638,499 per QALY gained. The probability that teduglutide was cost-effective if a decision-maker's WTP threshold was no more than $50,000 per QALY gained was 0%.

Table 3: CDR Reanalyses

			Total Costs	Incremental Cost of Teduglutide	Total QALYs	Incremental QALYs of Teduglutide	Incremental Cost per QALY
	Manufacturer's Base Case	BSC	$11,288,908	–	35.70	–	–
		Teduglutide + BSC	$15,388,255	$4,099,348	41.45	5.75	$713, 887
1.	Stopping rule changed from "achieving PS independence at any time" to "no stopping rule."	BSC	$11,288,853	–	35.74	–	–
		Teduglutide + BSC	$17,291,305	$6,002,452	41.23	5.49	$1,093,539
2.	Inclusion of only serious AE's identified by the clinical team in consultation with the clinical experts.	BSC	$11,288,941	–	35.78	–	–
		Teduglutide + BSC	$15,351,420	$4,062,479	41.63	5.85	$694,563
3.	Removal of caregiver disutilities.	BSC	$11,288,879	–	13.13	–	–
		Teduglutide + BSC	$15,417,989	$4,129,109	16.69	3.57	$1,158,144
4.	CADTH Base Case (combining 1 to 4).	BSC	$11,289,057	–	13.22	–	–
		Teduglutide + BSC	$17,240,361	$5,951,304	16.85	3.63	$1,638,499

AE= adverse events; BSC = best supportive care; PS =parenteral support; QALY = quality-adjusted life-year.

Note: The model results were stable over multiple model runs.

As noted above, it remains uncertain whether and when patients would discontinue treatment due to treatment response. Given these concerns, a scenario analysis was conducted applying the stopping rule assumed in the manufacturer's base case. In this scenario, with a stopping rule applied at any time when patients achieved PS independence and which assumed patients do not require further retreatment with teduglutide, the ICUR decreased to $1,106,536 per QALY.

CADTH undertook a price-reduction analysis based on the manufacturer submitted and CADTH base-case analyses (Table 4). A price reduction of 71% would be required to reach a WTP under the threshold of $50,000 per QALY gained.

Table 4: CDR Reanalysis of Price-Reduction Scenarios

ICURs of Teduglutide + BSC vs. BSC ($/QALY)		
Price	**Base-case analysis submitted by manufacturer**	**Reanalysis by CADTH**
Submitted	$691,962	$1,638,499
10% reduction	$612,333	$1,417,216
20% reduction	$498,584	$1,191,295
30% reduction	$380,724	$964,268
40% reduction	$269,361	$732,117
50% reduction	$161,932	$713,887
60% reduction	**$48,517**	$284,754
70% reduction	Dominant	**$56,500**
71% reduction	Dominant	$35,762
80% reduction	Dominant	Dominant
90% reduction	Dominant	Dominant

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Issues for Consideration

- Feedback from the clinical panel consulted by CADTH indicated that other important outcome measures are relevant in clinical practice to show an improvement toward a patient's treatment goals. The clinical panel indicated that the ability to reduce infusion time/fluid volume required from PN, a reduction in calories from PN while maintaining growth, and a reduction in the number of PN hours may all play a role in reducing complications. The economic analysis does not fully consider all these important outcome measures.
- The clinical panel consulted by CADTH indicated that patients may be at risk of developing teduglutide-specific antibodies with long-term treatment, which is likely among patients who are treated with therapeutic proteins. Experts noted that antibody development should be included as a criterion for treatment discontinuation in addition to other criteria for discontinuation. In Study 006, antibody development was reported in a total of eight patients within the low and high dose teduglutide groups. The economic analysis did not consider antibody development as part of the stopping rule criteria for treatment discontinuation.
- Clinical experts consulted by CADTH advised that the societal perspective should be considered given the substantial indirect costs and resources incurred by patients and their families. Although this was not a noted concern in the patient input received by CADTH, a societal perspective to the CADTH base case that explores the impact on caregivers' HRQoL is presented in Appendix 5 as a scenario analysis. The manufacturer's model does not permit the full exploration of a societal perspective, as other potentially relevant components (e.g., productivity costs, costs to patients and/or informal caregivers) were not model inputs.
- The product monograph for teduglutide states that a physician should weigh a patient at each visit to determine the daily dose to be administered until the next visit. The clinical experts consulted by CADTH indicated that the treatment dose may be reassessed on a monthly basis, especially for patients less than eight years of age whose rate of intestinal

growth has not plateaued, although they do not expect this to occur outside of regularly scheduled follow-up visits.

- Teduglutide may be administered either in a specialized medical clinic or at home by caregivers. Although the manufacturer's model only assumed one nurse-led appointment would be required to provide training to patients and their caregivers about how to self-administer teduglutide, clinical experts consulted by CADTH noted that a one-time session may not be sufficient. Although the cost of training may have been underestimated in the manufacturer's model, this is unlikely to have a considerable impact on the overall ICER.

Patient Input

Input was received from one patient group, the Gastrointestinal (GI) Society, who interviewed two clinicians and one caregiver and gathered published information. The patient group described that limitations brought on by SBS restricted social interactions, which resulted in stress, anxiety, and depression. Patients' quality of life was especially impacted from being unable to participate in common childhood social activities such as play, school, and engaging in social gatherings. Furthermore, the patient group reported that physiological symptoms negatively impacted all aspects of a child's life. For example, additional discomfort, fatigue, and pain were brought on by feeding equipment and controlled feeding schedules. Utilities in the manufacturer's model were elicited based on health state vignettes that were partly structured according to the EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression),[11,12] with further condition, symptom, and treatment-specific descriptions. The vignettes therefore partly captured the physiological and social impacts that would be expected with the different PS health states.

Current therapy for SBS includes one or a combination of total parenteral nutrition, EN, dietary adjustments, and surgery (e.g., intestinal transplantation).[18] EN broadly refers to the delivery of nutrients and calories to fulfill some or all of an individual's caloric requirements through the GI tract directly (i.e., tube feeding).[18] Parenteral nutrition is a method that delivers nutrients and calories into a vein for individuals whose GI tract is functioning sub-optimally. The patient group further identified AEs related to SBS and enteral feeding. Specific to enteral feeding, AEs experienced by patients included gastroesophageal reflux disease, abdominal bloating, cramps, nausea, diarrhea, constipation, and re-feeding syndrome. However, as noted above, enteral feeding was not considered within the submitted model.

Caregiver burden was not mentioned in the patient input submission.

Conclusions

A number of key limitations identified in the manufacturer's model had a large impact on the cost-effectiveness of teduglutide with BSC. CADTH's findings remained aligned with the manufacturer's: the addition of teduglutide to BSC is not a cost-effective option at a cost-effectiveness threshold of $50,000 per QALY. In CADTH's base case, teduglutide plus BSC was associated with an ICUR of $1,638,499 per QALY gained compared with BSC in pediatric patients with SBS. A price reduction of 71% would be required to achieve an ICUR below a WTP threshold of $50,000 per QALY. However, depending on the stopping rule, the ICUR may reduce to $1,106,536 per QALY gained if patients were assumed to never return to treatment after achieving their initial response.

Considerable uncertainty remains on the treatment effects of teduglutide plus BSC compared with BSC alone and the expected natural history of pediatric patients with this condition. The economic model was overall informed by a less robust clinical evidence base for the pediatric population than previously reviewed by CADTH. Limited natural history data resulted in a heavy reliance on assumptions, and limitations to the clinical trial design included small sample sizes, non-randomized comparisons, significant between-group heterogeneity, and short follow-up periods. All these could not be addressed by CADTH and interpretation of the economic results therefore warrants careful consideration.

Appendix 1: Cost Comparison

The comparators presented in Table 5 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 5: CDR Cost Comparison Table for Treatments for Short Bowel Syndrome

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Teduglutide (Revestive)	**5 mg/vial**	**Pre-filled syringe[a]**	**$904.0000[b]**	**0.05 mg/kg SC once daily**	**$904.00**	**$329,960**
	Administration		**PS Requirement**		**Cost per Day ($)**	**Annual Cost ($)**
Parenteral support[c]	IV administration, either by caregiver or nurse[d]		1 day to 7 days per week		$271.24 to $881.52	$99,002 to $321,755

IV = intravenous; SC = subcutaneous.

[a] Teduglutide is available as a single-use vial. If a full vial is not used, then the remaining dose is discarded. Dosage is dependent upon body weight. Only when a patient weighs more than 100 kg will a second vial be required.

[b] Manufacturer submitted price.[2]

[c] Calculated by the manufacturer, based on the study by Kosar et al. (2016).[10]

[d] Although treatment costs differ by mode of administration, the study by Kosar et al. (2016) did not specify how these costs may differ.

Appendix 2: Summary of Key Outcomes

Table 6: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Teduglutide + BSC Relative to BSC alone?

Teduglutide + BSC vs. BSC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					✓	
Drug treatment costs alone					✓	
Clinical outcomes		✓				
Quality of life		✓				
Incremental CE ratio (CADTH reanalysis)	Manufacturer's base case: $713,887 per QALY CADTH base case: $1,638,499 per QALY					

BSC = best supportive care; CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year; vs. = versus.

Appendix 3: Additional Information

Table 7: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			✓

Comments
Reviewer to provide comments if checking "no"
	• The base case in the economic model (and that produced in the manufacturer's reported results) was unclearly described or different than the settings that were described in the manufacturer's report. This included:
	  ○ Across the manufacturer's report states, a time horizon of both 94 years and 96 years is claimed.
	  ○ Age-dependent population utility values are switched on (in the base case) although the manufacturer's report describes these as being an optional setting.
	  ○ It was unclear whether serious AEs or all AEs occurring > 5% would be included in the base case based on the manufacturer's report.
	  ○ The manufacturer's report stated that the teduglutide AE rates were sourced from Study 006 while AEs in the placebo arm were sourced from the STEPS trial. However, in the base case, AE data for both teduglutide and placebo arms were extracted from Study 006.
	• Base case reset button does not reset to their described base case:
	  ○ Default discount rate is set equal to 3.5% rather than 1.5%.
	  ○ Intestinal transplantation turned on (report states intestinal transplantation is a structural feature that is off in the base case).
	• Several errors were noted with the manufacturer's submitted model:
	  ○ Regarding the best statistical fit of parametric survival curves to extrapolated data, the manufacturer incorrectly added glycated hemoglobin (AIC) values from different populations (PS independent and PS dependent) to create a combined statistic of best fit for the entire population. AIC should not be combined across datasets.
	  ○ Incorrect rate to probability conversion for AEs: 24-week probabilities were simply divided by 6 to obtain 28-day probabilities.
	  ○ Within the "PF.Teduglutide" worksheet, an error was found in the formula calculating total PS health state costs (GT13:GT1265). The correct cell (C13) has not been referenced in the formula for the time component. It should reference cycle length [days] rather than time in years [D13] as currently inputted.
	• There is an execution error with the time horizon in the economic model so that varying time horizons cannot be executed in the economic model.		

Was the material included (content) sufficient?		✓	
Comments Reviewer to provide comments if checking "poor"	None		
Was the submission well organized and was information easy to locate?			✓
Comments Reviewer to provide comments if checking "poor"	The manufacturer's report was not very well organized; the description of the base case and information on additional features of the model did not align well with the submitted economic model (see above).		

Table 8: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CDR
☐ Adaptation of Global model/Canadian model done by the manufacturer
☐ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

No reviews of teduglutide by other health technology agencies were completed at the time of this review for the requested CDR indication. Teduglutide is currently under review by National Institute for Health and Care Excellence (NICE).[19]

Appendix 5: Reviewer Worksheets

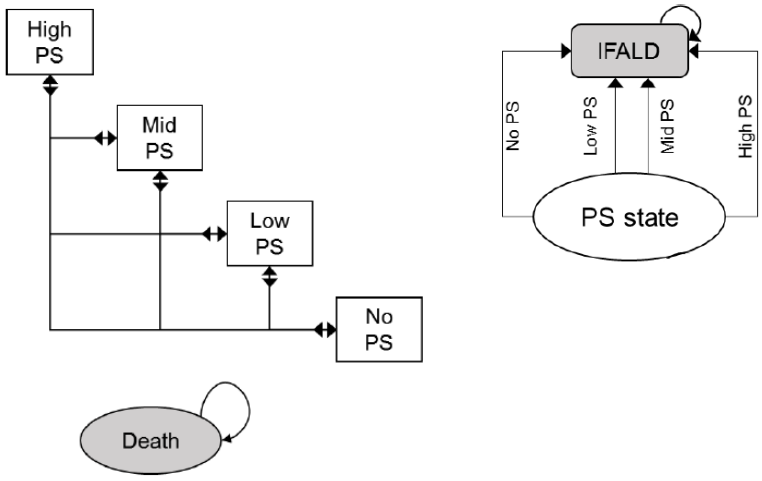
Manufacturer's Model Structure

The manufacturer constructed a Markov model (Figure 1) to compare teduglutide plus best supportive care (BSC) with BSC alone for the treatment of pediatric patients with short bowel syndrome (SBS).[2] The Markov model simulated patients' needs for parenteral support (PS) over a lifetime. The Markov model consisted of four PS health states, and one death health state (an absorbing state that patients cannot leave). Each PS state described a range of days per week that a patient is dependent on PS within the model cycle (with model cycle defined as a 28-day period). Patients entered PS health states according to the following classification:

- "PS0" state: independent of PS (i.e., a patient requires no PS)
- "Low PS" state: patient requires PS 1 day to 3 days per week
- "Mid PS" state: patient requires PS 4 days to 5 days per week
- "High PS" state: patient requires PS 6 days to 7 days per week.

Patients can transition from any PS state to any other PS state, remain in their existing PS state, or die. Patients can develop intestinal failure-associated liver disease (IFALD) from any PS state in the model and this transition probability is dependent on PS state. Patients entered the model according to the baseline distribution of PS health states evidenced by trial data.

Figure 1: Manufacturer's Base-Case Model Diagram



IFALD = intestinal failure-associated liver disease; PS = parenteral support.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 9: Data Sources

Data Input	Description of Data Source	Comment[a]
Baseline characteristics	Patient characteristics and baseline distributions were based on Study 006.	Appropriate despite clinical experts consulted on this review noting that Study 006 exclusion criteria were restrictive (eligibility criteria represent approximately 25% to 30% of the target population).
Efficacy	Efficacy of teduglutide and SOC were based on TED-C14-006.	Efficacy was modelled as the number of days per week that a patient required PS, separated into the four categories reflecting the model's PS health states. For the placebo (SOC) arm of Study 006, there were no observed transitions between the PS health states. Patients on BSC remained in the same health state over model cycles. According to clinical experts consulted by CADTH, spontaneous recovery is not expected in patients once growth in the body has stopped.
	Long-term PS transitions (> 24 weeks) were extrapolated based on assumptions.	Inappropriate. For the teduglutide arm, the transition probabilities between week 12 and week 24 (i.e., the last 3 months of the trial) were reapplied until the end of the second modelled year. Clinical experts consulted by CADTH noted uncertainty with this approach given the paucity of data. It remains unknown whether patients who are PS independent or dependent will continue to experience PS improvements over time at the rate of improvement demonstrated in the last three months of the trial. Assumptions to the BSC arm were also inappropriate. See Limitations of Manufacturer's Submission section within the main report for details.
Natural history	The manufacturer submitted additional scenario analyses to model rare health complications that could result: CKD and ITx.	Appropriate for CKD and ITx to be excluded from the base case.
Time horizon	A lifetime horizon (up to 100 years of age) was assumed in the base case.	Appropriate.
Utilities	PS health state disutility values were derived from a vignette study of an adult population conducted in the UK.[11,12]	No published utility values were available for the target population. The vignette study reported disutilities by specific number of days per week requiring PS. To obtain disutility values corresponding to the model's health states (i.e., range of days per week requiring PS), a simple average was calculated. The validity of this approach is uncertain and CADTH could not assess the impact of this limitation.
	Age-dependent general population utility values were sourced from the UK and were used to adjust utility values for the age of the patient cohort over the course of the model time horizon.[20]	Appropriate although Canadian sources would have been preferred. Inappropriate to include carer disutilities under a public payer perspective.

Data Input	Description of Data Source	Comment[a]
	Carer disutilities, based on a Delphi panel study in adults and a UK caregiver survey (ICON study).[2] Disutility value associated with IFALD was informed by the UK catalogue of EQ-5D scores for a range of conditions reported by Sullivan et al. (2011).[5] Utilities associated with AEs were informed by published literature.[5,6]	Likely inappropriate although this parameter had negligible impacts on model results.
AEs	In the base case, the model includes serious AEs only sourced from Study 006. As an option, it provides the flexibility to incorporate all AEs. Rates of AEs associated with teduglutide were obtained from Study 006.	Inappropriate. See Limitations of Manufacturer's Submission section within the main report for details.
Mortality	Hazard ratio for OS in PS-dependent patients versus PS-independent patients was based on Fullerton et al.[4] OS curves were fitted parametrically; the Weibull distribution was assumed to provide the best fit. Mortality was constrained so that it would not be lower than the background all-cause mortality estimated from Statistics Canada life tables.[14]	Inappropriate. See Limitations of Manufacturer's Submission section within the main report for details.
Complications	The manufacturer assumed that IFALD can develop in all PS-dependent patients in the base case. Its incidence is dependent on the PS state a patient is in. Patients with IFALD can transition between PS health states at equal rates to patients without IFALD. The rates of liver failure were assumed to be identical to the rates in adults and were estimated by experts in the Delphi meeting.[2] Progression of liver disease was assumed to be the same between pediatric and adult populations due to lack of data (based on Cavicchi et al. 2000).[21]	Likely reasonable. These parameters had negligible impacts on the model's results.
Resource use and costs		
Drug	Price of teduglutide based on manufacturer's price.[2]	Appropriate.
Administration	Model assumes administration of teduglutide is associated with no specific administration costs, except for one initial nurse-led appointment to instruct patients on how to self-administer the treatment. This was calculated based upon an hourly cost of $35 for a consultation with a community nurse.	Potentially underestimates administration costs. Although the manufacturer indicated there are no administration needs expected with teduglutide, except for a single nurse-led appointment to train patient on how to self-administer the treatment, clinical experts consulted on this review noted that training may be iterative.
AEs	Costs for the management of AEs were derived from OCCI and OHIP (Table 19).[7,8]	Appropriate.
Parenteral support	Costs for PS were derived from Kosar et al. (2016).[10]	Conservative. Likely underestimates total PS costs. The manufacturer only includes the costs of home

Data Input	Description of Data Source	Comment[a]
		PS but does not include costs of in-hospital PS as data on the latter is unknown.
Other costs	IFALD: Costs for IFALD was derived from Wong et al. (2016).[22]	Likely unreasonable but unlikely to impact the model. The costs reflect the cost in a hepatitis C population. The model was not sensitive to change to this model parameter.

AE = adverse events; CKD = chronic kidney disease; EQ-5D= EuroQol 5-Dimensions questionnaire; IFALD = intestinal failure-associated liver disease; ITx = intestinal transplantation; OCCI = Ontario Case Costing Initiative; OHIP = Ontario Health Insurance Plan; OS = overall survival; PS = parenteral support.

Table 10: Manufacturer's Key Assumptions

Assumption	Comment
Use of teduglutide is not expected to provide a difference in the use of symptom-relief medication.	Conservative assumption.
Enteral autonomy was defined as patients achieving PS independence, reflecting the definition in Study 006.	Inappropriate, as confirmed by clinical experts consulted by CADTH. Patients who achieve PS independence require additional support until they achieve enteral autonomy. A patient may be PS independent without the achievement of enteral autonomy.
Treatment is stopped if a patient achieves PS independence at any point in time over the 24 weeks (response) or if a patient fails to achieve a 20% PS volume reduction at the end of 24 weeks compared with baseline (non-response).	Stopping rule for non-response was appropriate although stopping rule for response was considered inappropriate by clinical experts consulted by CADTH. See Key Limitations within the main report for details.
The manufacturer assumed that ITx is not an option for patients who receive SOC.	Potentially inappropriate. According to the clinical experts consulted by CADTH, the role of ITx has diminished given the emergence of highly specialized medical centres and the high mortality rates associated with ITx. There is further no published evidence on the efficacy of ITx and its long-term prognosis. However, clinical experts noted significant costs and quality of life impacts with ITx that may be important to consider. As such, CADTH conducted a scenario analysis using the manufacturer's assumptions, including that the prognosis of ITx would be similar between adults and children.
Vial sharing is not assumed.	Conservative assumption.

ITx = intestinal transplantation; PS = parenteral support; SOC = standard of care.

Table 11: Manufacturer's Base-Case Results: Total Costs

Cost Parameter	Teduglutide + BSC	BSC	Incremental
Teduglutide	$6,339,925	$0	$6,339,925
Administration training	$35	$0	$35
Colonoscopy	$789	$0	$789
PS	$8,815,803	$11,258,262	–$2,442,459
ITx	$0	$0	$0
Liver complications	$24,073	$30,664	–$6,592
Adverse events	$131,827	$0	$131,827
Total costs	**$15,312,452**	**$11,288,926**	**$4,023,527**

BSC = best supportive care; ITx = intestinal transplantation; PS = parenteral support.

Note: Summary of total costs by resource type were derived from manufacturer's deterministic base-case results.

Source: Manufacturer's pharmacoeconomic submission.[2]

CADTH Common Drug Review Scenario Analyses

Figure 2: CADTH Base-Case Cost-Effectiveness Acceptability Curve

Several scenario analyses were undertaken to consider alternate scenarios of the CADTH base-case reanalysis (Table 12):

1. Inclusion of intestinal transplantation: The manufacturer's base case did not include ITx, given its rarity and the limited clinical evidence on its treatment effects. Although clinical experts consulted by CADTH similarly noted a decline in performing this procedure, they noted the impact of significant costs and quality of life with intestinal transplant. CADTH conducted a scenario analysis including this treatment option in patients with SBS.

2. Changing the distributional forms of the survival curves from the Weibull distribution to either: (a) a gamma distribution or (b) a lognormal distribution.
3. Removing the development of IFALD: The manufacturer's model included IFALD as an important but rare outcome of PS. Feedback from clinical experts consulted by CADTH indicated that with continued improvements in the provision of PS, the risk of IFALD is expected to further decrease. CADTH assessed the impact of removing IFALD in a scenario analysis.
4. Changing the stopping rule to allow patients to achieve PS independence at any time.
5. Including caregiver disutilities to broadly consider the impacts on patients' caregivers.

Results of the CADTH reanalysis can be found in Table 12. CADTH assessed the impact of the gamma and lognormal distributions and found that the model was less sensitive to changes in the parametric distributional form selected to model OS. Negligible impacts on the model were observed with the removal of IFALD, while the model was most sensitive to the inclusion of intestinal transplantation, the addition of a stopping rule for responders, and the incorporation of caregiver disutilities. If intestinal transplantation was modelled as a subsequent treatment option, the ICUR reduced compared with the CADTH base case as incremental costs decreased given it was assumed that patients would no longer be receiving teduglutide following intestinal transplant. The ICUR decreased compared with the CADTH base case with the inclusion of caregiver disutilities, favouring teduglutide as patients on teduglutide required fewer days of PS each week.

Table 12: Results of CADTH Scenario Reanalyses

	Scenario		Total Costs	Incremental Cost of Teduglutide	Total QALYs	Incremental QALYs of Teduglutide	Incremental Cost per QALY
1.	Inclusion of intestinal transplantation	BSC	$6,378,676	–	10.90	–	–
		Teduglutide + BSC	$11,070,862	$4,692,186	14.75	3.85	$1,219,872
2a.	Changed Weibull distribution to gamma distribution	BSC	$14,385,466	–	16.50	–	–
		Teduglutide + BSC	$21,482,766	$7,097,300	20.06	3.56	$1,992,762
2b.	Changed Weibull distribution to lognormal distribution	BSC	$11,289,057	–	13.22	–	–
		Teduglutide + BSC	$17,240,361	$5,951,304	16.85	3.63	$1,638,499
3.	Removal of intestinal failure-associated liver disease	BSC	$11,258,262	–	13.56	–	–
		Teduglutide + BSC	$17,210,640	$5,952,378	17.22	3.67	$1,622,541
4.	Achieving PS independence	BSC	$11,289,017	–	13.27	–	–
		Teduglutide + BSC	$15,383,713	$4,094,696	16.97	3.70	$1,106,536
5.	Inclusion of caregiver utilities	BSC	$11,289,165	–	35.83	–	–
		Teduglutide + BSC	$17,244,197	$5,955,033	41.44	5.61	$1,062,001

BSC = best supportive care; PS = parenteral support; QALY = quality-adjusted life-year.

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