Common Drug Review
Pharmacoeconomic Review Report

August 2016

Drug	Teduglutide (Revestive)
Indication	For the treatment of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support
Listing request	As per indication
Dosage form(s)	5 mg vials for subcutaneous injection
NOC date	September 04, 2015
Manufacturer	Shire Pharma Canada ULC/NPS Pharma Holdings Ltd.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
GLP-2	glucagon-like peptide-2
ICUR	incremental cost-utility ratio
IFALD	intestinal failure–related liver disease
PN	parenteral nutrition
PS	parenteral support
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
SBS	short bowel syndrome
SOC	standard of care
STEPS	Study of Teduglutide Effectiveness in PS-Dependent Short Bowel Syndrome
TED	teduglutide
TTO	time trade-off

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Teduglutide 0.05 mg/kg/day
Study Question	To assess the economic impact of teduglutide for the treatment of SBS in Canada
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with SBS who are dependent on PS
Treatment	Teduglutide 0.05 mg/kg/day administered subcutaneously
Outcome	QALY
Comparator	Standard of care, consisting of sufficient volume of parenteral nutrition or support and management of symptoms
Perspective	Canadian Ministry of Health
Time Horizon	40 years
Results for Base Case	ICUR = $1,600,145 per QALY
Key Limitations	CDR noted the following limitations with the manufacturer's 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. This stopping rule was used in the teduglutide clinical trials and was confirmed to be appropriate by the clinical expert consulted by CDR. Not applying this stopping rule leads to cost-effectiveness results favouring teduglutide. • The health state utilities used in the model were from a Web-based unpublished survey of panellists 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 UK population and was not specific to PS-related liver diseases; the generalization of these data to the current context is questionable. • The percentage of patients who self-administer PS treatment appeared to be arbitrarily selected and was not justified by the manufacturer. This was tested by CDR. • A technical limitation of the submitted model was that it erroneously updated some parameters when conducting sensitivity analyses, thereby undermining the confidence in the model's sensitivity analysis results.
CDR Estimate(s)	• CDR performed several reanalyses to test the above-mentioned limitations. • The model results were sensitive to applying the stopping rule for teduglutide. • A scenario in which patients discontinued teduglutide after 24 weeks due to not achieving a 20% reduction in PS volume represents the CDR best estimate, and resulted in a reduced ICUR for teduglutide compared with standard of care of $1,589,764 per QALY. • Difficulty in assessing the uncertainty over the PS health state utility values and the extent to which they reflect the value of teduglutide in treating SBS warrants cautious interpretation of model outcomes and results — the internal validity of these utility values may be questioned and the external validity was not demonstrated; potentially, most appropriate values may lead to a much higher ICUR result.

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; PS = parenteral support; QALY = quality-adjusted life-year; SBS = short bowel syndrome.
Source: Manufacturer's pharmacoeconomic submission.[1]

EXECUTIVE SUMMARY

Background

Teduglutide is a glucagon-like peptide-2 (GLP-2) analogue indicated for the treatment of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support (PS).[2] The recommended dose of teduglutide is 0.05 mg/kg/day via subcutaneous administration.[2] The manufacturer submitted a confidential price of $[redacted] per 5 mg vial,[1] which corresponds to an annual cost of $[redacted] for patients weighing up to 100 kg. Patients weighing more than 100 kg will incur an annual cost of $[redacted]. The manufacturer is requesting reimbursement in line with the Health Canada indication.

A cost-utility analysis was submitted comparing teduglutide to standard of care (SOC) in adult patients with SBS who are PS-dependent. SOC 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.[3,4] The utility inputs for the PS health states were based on a Canadian study conducted by the manufacturer via a Web-based survey for the general population.[1] For health state costs, the data source to estimate the cost of PS was a Canadian economic study by Marshall et al. (2005) that reported the mean per diem cost of PS administration by a nurse at patients' homes.[5] Probabilities of intestinal failure–related liver disease (IFALD) from PS were derived from the literature.[6] Adverse event rates were derived from the STEPS trials,[3,4] with costs from the Ontario Case Costing Initiative (OCCI)[7] and the Ontario Schedule of Benefits (2015).[7,8] The analysis was conducted from the perspective of a Canadian publicly funded health care system assuming a 40-year time horizon.

The manufacturer reports an incremental cost-utility ratio (ICUR) for teduglutide compared with SOC of $1,600,145 per quality-adjusted life-year (QALY) gained. Results of sensitivity analysis were sensitive to varying the time horizon, rates of adverse events, and rates of IFALD. Results of the probabilistic sensitivity analysis (PSA) indicated that teduglutide has a 50% probability of being cost-effective at a threshold of $1,960,000 per QALY gained.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several limitations with the submitted economic analysis.

The key limitation was that 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. The stopping rule was applied in the STEPS clinical trial program and was judged appropriate by the clinical expert consulted by CDR.

Other limitations included the uncertainty with the health state utility values, the disutility from IFALD, and the assumed proportion of patients' self-administered PS. CDR noted that the PS health state utilities were based on an industry-funded study (unpublished) that obtained the values through a Web-based survey. The manufacturer did not provide sufficient information over the elicitation or scoring processes, which made it challenging to validate the utilities used in the model. It was noted that the differences in utility values were notable and may overestimate the differences among health states. CDR also identified a technical limitation in which the model erroneously updated some parameters when conducting sensitivity analyses; this warranted cautious consideration of model results.

CDR reanalyses taking into consideration independently all limitations suggested the ICUR for teduglutide compared with SOC ranged from $1,588,364 to $1,666,666 per QALY.

Conclusions

CDR reanalyses that included the stopping rule, applied in the clinical trial program for teduglutide and judged appropriate by the clinical expert for this review, resulted in an ICUR for teduglutide of $1,589,764 per QALY. Applying the teduglutide stopping rule while varying the health utility values resulted in an ICUR of $1,607,126. These ICURs for teduglutide reflect the uncertainty over the utilities used to value the effect of teduglutide in reducing PS, suggesting that the predicted QALY gains with teduglutide are likely overestimated; this is in association with the high costs associated with teduglutide therapy as add-on to already costly PS use. The uncertainty with the predicted QALY benefits warrants cautious consideration when interpreting the results of the analyses.

Based on CDR reanalyses varying the health state utilities and applying (or not) the stopping rule, teduglutide would require a reduction in price of approximately 83% to reach ICURs of $37,597 and $38,633 per QALY compared with SOC. It should be emphasized that reducing the QALY gain from reduction of PS usage, driven by the PS health state utilities used in the model, which are associated with high uncertainty, would lead to a higher ICUR.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis evaluating teduglutide compared with standard of care (SOC) in adult patients with short bowel syndrome (SBS) who are dependent on parenteral support (PS). The base-case analysis used a time horizon of 40 years using the Canadian public payer perspective.[1]

The submitted model consisted of eight PS-related health states, and one death health state (an absorbing state that patients cannot leave) (Figure 1). The eight PS states describe the average number of days per week that a patient is dependent on PS in that model cycle (with a model cycle defined as a 28-day period). A patient in the "PS0" state is independent of PS, requiring zero days of PS in that cycle. The PS requirements increased to a maximum "PS7" state, where patients require PS seven days a week. Patients are able to transition between model cycles from any PS state to any other PS state or can remain in their existing PS state. Patients can develop intestinal failure–related liver disease (IFALD) from any PS health state in the model except PS0. The 28-day length of each Markov cycle was assumed to be consistent with the assessment schedule in the STEPS trial, where patient PS requirements were recorded every 28 days, hence enabling the estimation of the monthly transition probabilities between PS states.[1] Assessments were made every three months in the follow-up STEPS-2 trial; this results in patients transitioning between the PS health states only every three months after the first nine months. The manufacturer's base-case analysis assumed a 40-year time horizon.

Efficacy data in terms of reduction in PS use for teduglutide and SOC in patients with SBS were derived from the STEPS trials.[3,4] The utility inputs for the PS health states were based on a Canadian study conducted by the manufacturer that analyzed responses from 799 participants via a Web-based survey.[1] The utility values for IFALD and adverse events were derived from published literature.[9,10] Probabilities of IFALD were taken from the literature,[6] and adverse event rates for compared interventions were taken from the STEPS trials.[3,4] Population utility norms for the UK were included in the model to provide estimates of general population utility, which vary by age and were therefore used to adjust utility values for the age of the patient cohort over the course of the model time horizon.[11]

For health state costs, the data source to estimate the cost of PS was a Canadian economic study by Marshall et al. (2005) that reported the mean per diem cost of PS administration by a nurse at patients' homes. The cost of self-administered PS support was calculated by deducting the cost related to nurse care.[5] Costs associated with the management of IFALD were based on the Ontario Case Costing Initiative (OCCI).[7] Costs for the management of adverse events were derived from the OCCI and Ontario Schedule of Benefits (2015).[7,8] Costs were expressed in 2015 Canadian dollars and the analyses were conducted from the perspective of a Canadian publicly funded health care system assuming a 40-year time horizon. Probabilistic and univariate sensitivity analyses were conducted to estimate the uncertainty associated with the data. Costs and outcomes beyond one year were discounted at 5%.

2. MANUFACTURER'S BASE CASE

Using a 40-year time horizon, teduglutide resulted in an ICUR of $1,600,145 per quality-adjusted life-year (QALY) gained compared with SOC (Table 2).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Costs ($)	Incremental Costs ($)	LYs	Incremental LYs	QALYs	Incremental QALYs	ICUR ($/QALY)
SOC	1,227,500.40		7.81		2.35		
TED	3,584,110.57	2,356,610.16	8.39	0.58	3.82	1.47	1,600,145.36

ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year; SOC = standard of care; TED = teduglutide.
Source: Adapted from manufacturer's pharmacoeconomic submission, Table 18 (page 42).[1]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

In addition to the base-case analysis, the manufacturer conducted probabilistic analyses and one-way sensitivity analyses to assess the uncertainty associated with the model parameters, inputs, and assumptions. The results of the manufacturer's one-way sensitivity analyses indicate that the model results are most sensitive to the model time horizon, rates of IFALD, and rates of adverse events. The results were also sensitive to the selected survival curve used in the model. The manufacturer performed the probabilistic sensitivity analysis (PSA) by conducting 10,000 Monte Carlo simulations in which values of key parameters were drawn randomly and independently from the parameter distributions. Beta distributions were used for utilities and adverse events, while gamma distributions were used for costs. Transition probabilities were included in the PSA using a Dirichlet distribution, with an informed prior assumption that patients can either stay in their present PS state or move up or down by one state. The results of the manufacturer's PSA indicate that at a willingness to pay of $1,960,000 per QALY gained, teduglutide has a 50% probability of being cost-effective.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Teduglutide stopping rule:** Based on the STEPS clinical trials program, patients who did not experience at least a 20% PS reduction after 24 weeks would discontinue teduglutide and then receive PS only.[3] This stopping rule was confirmed by the CDR clinical expert but had not been included in the manufacturer's base case and sensitivity analyses. According to the clinical expert consulted by CDR, although response to teduglutide may be detected as early as six weeks into treatment, it is unlikely that any previously unseen or spontaneous response would be reported beyond the 24 weeks of treatment.
- **PS health state utilities:** The PS health state utilities in the model were based on values from an industry-funded time trade-off (TTO) study (unpublished) that obtained the health state utility values through a Web-based survey.[1] Data from 799 respondents from the general population were used to derive the health state utilities. Respondents were split into three groups and were tasked with deriving utility values for each of the nine health states (PS0 to PS7, with PS7 having two sub-states, high and low). Each group was tasked with scoring three out of the nine health states, where each selection included a mild, moderate, and severe health state (e.g., Group A: PS0, PS3, and PS6; Group B: PS2, PS5, and PS7 high). Values from the survey were fitted to develop a trend line across

the health states, which revealed discrepancies that warranted further information not provided by the manufacturer in the submitted report. Based on this exercise, utility values ranged from 0.39 (PS7) to 0.74 (PS0). It is unclear whether these utility values are an accurate reflection of the value that might be attributed to the different extent of PS use. Had respondents been asked about similar health states (e.g., PS3, PS4, and PS5), individuals might not have differentiated as significantly among them. As CDR was unable to identify any publicly available evidence on utility scores for SBS, a reanalysis was conducted using mean utility values directly from the study. Although the results were not significantly altered, the high uncertainty with the proposed PS health states utilities warrants further research.

- **Utility associated with IFALD:** The utility value associated with IFALD in the manufacturer's base-case model was derived from a study by Sullivan et al. (2011) that reported utility scores for a wide variety of chronic conditions in the UK population.[9] Although liver disease was included in the Sullivan et al. study, it was not specific to PS-related liver complications; i.e., the utility values in the study reflected liver complications of any cause, including PS-related liver disease.[9] In addition, the manufacturer did not provide a rationale for using the UK-based publication despite the availability of a US-based study (Sullivan et al. 2006) that reported preference weights reflecting the US community preferences or utilities.[12] These factors bring into question the appropriateness of using such a general utility value for IFALD and consequently raise uncertainty about the model results.
- **Administration of parenteral support:** The manufacturer's base-case model assumed that 50% of patients require nurse-led administration of PS, with the remaining 50% self-administering. This assumption was not justified by the manufacturer, nor was it confirmed to be correct by the clinical expert consulted by CDR — these proportions in real-life clinical practice are unknown. Self-administration of PS incurs a lower cost than nurse-led administration; therefore, an increase in the percentage of patients self-administering teduglutide is expected to lead to an increase in the ICUR of teduglutide compared with SOC.
- **Technical limitations with the submitted model:** CDR identified technical limitations with the submitted model that warrant cautious consideration of model results: when modifying some model parameters and assumptions, the model's ability to update and adjust the included inputs and values accordingly was inaccurate. Such a technical limitation undermines the confidence in the model's results.

5. CADTH COMMON DRUG REVIEW REANALYSES

5.1 Teduglutide stopping rule

CDR conducted reanalyses that activated the stopping rule for teduglutide patients in which patients who do not achieve a response of at least 20% reduction in PS volume would discontinue teduglutide treatment. Applying the stopping rule resulted in the ICUR of teduglutide to decrease to $1,589,764 per QALY gained (Table 11, Appendix IV).

5.2 Administration of parenteral support

CDR conducted one-way sensitivity analyses varying the percentage of patients self-administering PS from 25% to 75%. The ICUR was not significantly affected by varying the self-administration assumption (Table 12, Appendix IV).

5.2.1 PS health state utilities

The PS health state utility values were derived from the trend line resulting from fitting average utility data from responses to a Web-survey. As previously mentioned, no information was provided on

whether these PS health state utility values are an accurate reflection of the value that might be attributed to the different extent of PS use, and the method used to elicit these utility values is associated with high uncertainty. In addition, fitting the values to develop a trend line across health states revealed discrepancies that warranted further information that was not provided by the manufacturer. As CDR was unable to identify any publicly available evidence on utility scores for SBS, the reanalysis was conducted using mean utility values directly from the study. As the analysis was using the same data set, the ICUR, expectedly, was not significantly impacted (Table 13, Appendix IV).

5.2.2 Utility associated with IFALD

The utility value associated with IFALD in the manufacturer's base-case model was derived from a UK-specific study that reported utility scores for general liver complications without a specific utility value for PS-related liver complications. CDR conducted a reanalysis using an alternate utility value for liver disease from a publication by Sullivan et al. (2000) that also reflected general liver disorders. The ICUR for teduglutide compared with SOC increased to $1,666,666 per QALY (Table 14, Appendix IV).

5.2.3 Additional price reduction scenario

A price reduction analysis was conducted on the manufacturer's base-case analysis and on CDR's reanalyses, varying the health states utilities and applying (or not) the stopping rule for teduglutide. The results showed that a price reduction of approximately 83% would reduce the ICUR of teduglutide in the manufacturer's base-case analysis to $38,402 per QALY. Using CDR's reanalyses, a price reduction of approximately 83% would reduce the ICUR of teduglutide to $37,597 and $38,633 per QALY (Table 15, Appendix IV).

6. ISSUES FOR CONSIDERATION

- **Therapeutic need:** The standard care in SBS patients is mainly supportive and focuses on optimizing remnant intestinal function through dietary interventions, oral rehydration solutions, and antidiarrheal and antisecretory agents. Following resection, many SBS patients require the chronic use of PS to supplement and stabilize their hydration and nutritional needs. However, although PS can meet basic nutrition and fluid requirements, it does not improve the body's ability to absorb nutrients and may be associated with life-threatening complications (e.g., sepsis, blood clots, or liver damage), as well as reduced quality of life.[13-15] Teduglutide is expected to reduce the exposure to PS constituents administered to patients; however, the significant costs associated with teduglutide use compromise its attractiveness from an economic perspective.
- **Trial-based model**: The manufacturer's economic evaluation was based on the data reported in the STEPS trial; patient transitions throughout the model health states were informed by results from the periodic assessments during the clinical trial. Since patients' movements throughout clinical trials are not linearly proportional with time, it is expected that outcomes of the trial-based economic model, in terms of costs and benefits, may not be congruent with the expected results based on a priori assumptions and parameters. This is a critical characteristic of the submitted trial-based economic model for teduglutide and should be noted when relaying results of sensitivity analyses to decision-makers.
- **Reduction in parenteral nutrition days**: Transition probabilities in the economic model are based on the number of days of parenteral nutrition per week. According to the clinical expert consulted by CDR, the approach by which the number of days that parenteral nutrition is reduced varies by clinical practice and may not be a simple reduction in number of days or times per week. A recognized approach might be an initial reduction in daily parenteral volume that would be followed

by redistribution of the remaining volume into a reduced number of days per week. This variation in practice may not have been reflected in the STEPS trials and in the economic model.

6.1 Patient Input

The GI (Gastrointestinal) Society provided the patient input for this review. The patient group noted that patients expect teduglutide to control symptoms of SBS, reduce dependence on parenteral nutrition, and improve quality of life. The manufacturer's cost-utility analysis modelled the efficacy of teduglutide in reducing the frequency of parenteral nutrition and consequently improving quality of life.

7. CONCLUSIONS

Several limitations were identified with the submitted economic evaluation. The key limitation was that the teduglutide stopping rule was not applied despite being part of the study design of the STEPS trials and was confirmed by the clinical expert consulted by CDR as being reflective of clinical practice. CDR reanalysis that included the stopping rule resulted in an ICUR for teduglutide of $1,589,764 per QALY. When applying the stopping rule and varying the health state utilities, the ICUR for teduglutide increased to $1,607,126 per QALY. Other limitations identified included the uncertainty with the disutility from IFALD and the percentage of patients who self-administer PS. In assessing the PS health state utilities, several issues were raised over the internal validity of the utility values and the extent to which they reflect the actual value of PS reduction (external validity was not demonstrated), and as CDR was unable to identify any available evidence on utility scores for SBS, the clinical benefits and outcomes from this analysis need to be viewed with caution.

Based on the CDR reanalyses varying health state utilities and applying (or not) a stopping rule for teduglutide, teduglutide would require a reduction in price of approximately 83% to reach ICURs of $37,597 and $38,633 per QALY compared with SOC. It should again be emphasized that the cost-effectiveness analysis is associated with high uncertainty mostly from the utility values used for PS health states; a most appropriate ICUR resulting from the analysis may be much higher.

APPENDIX 1: COST COMPARISON

Feedback from the clinical expert consulted by the CADTH Common Drug Review (CDR) was that there is no relevant comparator for teduglutide. This takes into account that 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 3: COST COMPARISON TABLE FOR TREATMENTS FOR SHORT BOWEL SYNDROME

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Teduglutide (Revestive)	**5 mg powder plus 0.5 mL solvent**	**Powder in vial,[a] solvent in pre-filled syringe**	[redacted]	**0.05 mg/kg/day [b]**	[redacted]	[redacted]

	Administration	PS Requirement	Cost per Day ($)	Annual Cost ($)
Parenteral support unit cost calculation[c]	**Self-administration by the patient**	**5 days per week**	**402.47**	**105,002**
	Administration by a community nurse	**5 days per week**	**489.23**	**127,637**

Note: Cost of teduglutide based on manufacturer's confidential submitted price.[1]

[a] Teduglutide is available as a single-use vial — if a full vial is not used, then the remaining dose is discarded. Thus, wastage needs to be incorporated.

[b] Dosing is dependent upon body weight. The average body weight was assumed to be 65 kg to align with the STEPS clinical trial. Only when a patient weighs more than 100 kg will a second vial be required.[3]

[c] Source: Calculated by the manufacturer, based on the study by Marshall et al. (2005).[1,5]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS TEDUGLUTIDE + STANDARD OF CARE RELATIVE TO STANDARD OF CARE ALONE?

Teduglutide + SOC Versus SOC Alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$1,600,145 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life year; SOC = standard of care.
Note: Based on manufacturer's results.[1]

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 5: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well-organized and was information easy to locate?	X		
Comments	None		

TABLE 6: AUTHORS' INFORMATION

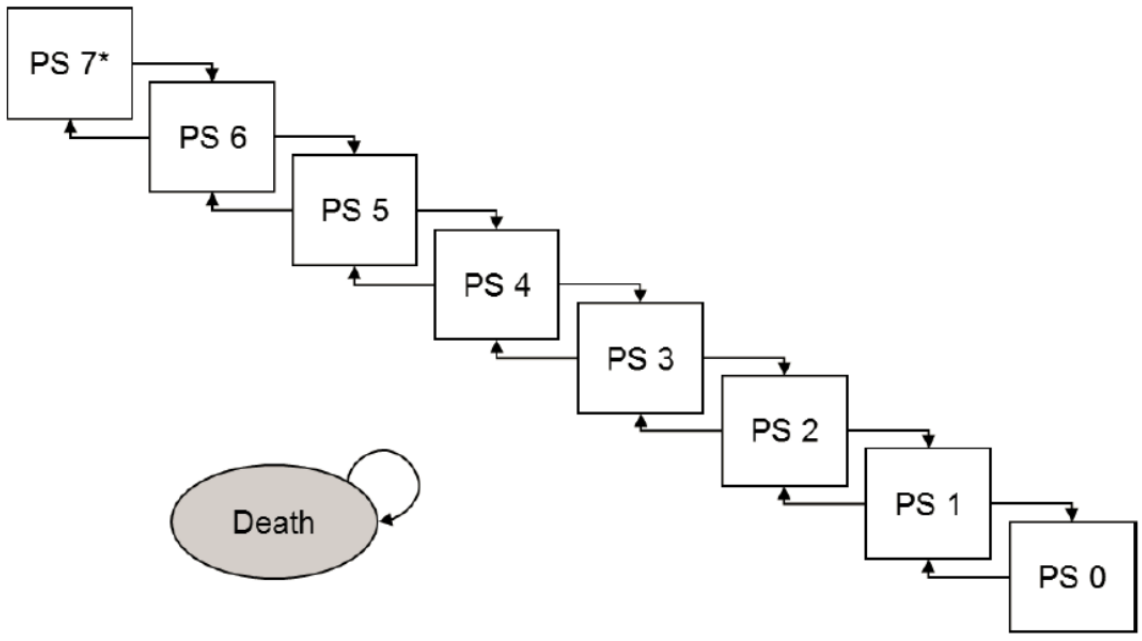
Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review			
☐ Adaptation of Global model/Canadian model done by the manufacturer ☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model 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: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer constructed a Markov transition model to compare teduglutide with standard of care (SOC) in the treatment of short bowel syndrome (SBS). The Markov model simulated patients' needs for parenteral support (PS) over a lifetime. The Markov model consisted of eight PS-related health states, and one death health state (an absorbing state that patients cannot leave). The eight PS states describe the average number of days per week that a patient is dependent on PS in that model cycle (with a model cycle defined as a 28-day period). A patient in the "PS0" state is independent of PS, requiring zero days of PS in that cycle. The PS requirements increased to a maximum "PS7" state, where patients require PS seven days a week. Patients are able to transition between model cycles from any PS state to any other PS state or can remain in their existing PS state. The most severe PS state, "PS7," is characterized by two sub-states relating to PS volume requirement to account for the small number of patients in the STEPS trial dependent on exceptionally high volume PS (≥ 4L per day), seven days a week.[1] Patients can develop intestinal failure–related liver disease (IFALD) from any PS health state in the model except PS0. IFALD is associated with PS and, therefore, no IFALD was assumed to be present in patients in the PS0 health state. As patients with IFALD could move between the PS health states, IFALD was not considered a separate health state. The 28-day length of each Markov cycle was consistent with the assessment schedule from the STEPS trial, where patient PS requirements were recorded every 28 days, hence enabling the estimation of the monthly transition probabilities between PS states.[a] Assessments were made every three months in the follow-up STEPS-2 trial; this results in patients transitioning between the PS health states only every three months after the first nine months. The manufacturer's base-case analysis assumed a 40-year time horizon.

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



*Composed of two sub-states based on volume of PS per day. The death health state is an absorbing state and can be entered from any state
Source: Manufacturer's pharmacoeconomic submission.[1]

TABLE 7: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Efficacy of teduglutide and SOC were based on the STEPS trial: A randomized 24-week trial assessing the efficacy of teduglutide compared with placebo for the treatment of PS-dependent SBS.[3] A 24-month single-arm follow-up study, STEPS-2, collected longer-term teduglutide data.[4]	Appropriate
Natural history	Patient characteristics and baseline distributions of patients were based on the STEPS clinical trial.[3]	Appropriate
Utilities	Utility values used for this economic evaluation were derived from a Canadian TTO study.[1] Population utility norms for the UK were included in the model to provide estimates of general population utility, which vary by age and were therefore used to adjust utility values for the age of the patient cohort over the course of the model time horizon.[11] The health state utility 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).[9] Utilities associated with AEs were informed by published literature.[9,10]	The utility associated with IFALD is that of general liver disorders and may not appropriately be reflective of incidents of IFALD attributed to parenteral nutrition.
Resource use		
AEs	AE rates were derived from STEPS and STEPS-2 trials.[3,4] Rates of IFALD are based on published literature (Cavicchi et al. 2000) that reported 2-year PS-related liver disease prevalence (defined by bilirubin greater than 60 and decompensation or fibrosis or cirrhosis on biopsy) in 90 patients who received home parenteral nutrition management.[6]	The AE rates associated with SOC were obtained from the placebo arm of STEPS, only; rates are not time-variable.
Mortality	Parametric survival curves fitted to data were taken from Amiot et al. (2013).[16] Background all-cause mortality over time was estimated from Statistics Canada life tables from 2009 to 2011, starting at the baseline age of patients in the model taken from the STEPS trials.[17,18]	
Costs		
Drug	Costs associated with PS was based on a Canadian study by Marshall et al. (2005).[5]	Appropriate
Administration	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. The training of patients is assumed to take 1 hour. The cost associated with this	Appropriate. Model allows the option to exclude the one-time training cost.

Data Input	Description of Data Source	Comment
	visit was based on the median hourly wage of a registered nurse in Quebec.[19]	Cost from Quebec not optimal.
AEs	Costs for the managements of AEs were derived from OCCI[7] and OHIP.[8]	
Colonoscopy	Colonoscopy costs were derived from the OCCI and OHIP.[7,8]	
IFALD	Costs associated with the management of IFALD was based on OCCI.[7]	

AE = adverse event; EQ5D = EuroQol Five-Dimensions Health-Related Quality of Life questionnaire; IFALD = intestinal failure–related liver disease; OCCI = Ontario Case Costing Initiative; OHIP = Ontario Health Insurance Plan; PS = parenteral support; SBS = short bowel syndrome; SOC = standard of care; STEPS = Study of Teduglutide Effectiveness in PS-Dependent Short Bowel Syndrome; TTO = time trade-off.

TABLE 8: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Transitions between PS health states based on STEPS and STEPS2 data	This assumption is likely appropriate. However, based on the clinical expert consulted by CDR, reduction in number of PS days is typically achieved via PN volume reduction at the initial stage, to be followed by redistribution of the total (reduced) PN volume over a shorter time period (i.e., less number of days). The approach outlined by the expert may be subjected to variation in clinical practice.
50% of patients can self-administer PS; 50% of patients require nurse-led administration	Uncertain. Cannot be confirmed by expert.
Extrapolation teduglutide patients after 30 months: Remain in same PS health state	Likely appropriate, as confirmed by the clinical expert consulted by CDR, despite the absence of longer-term data.
Extrapolation SOC and discontinued patients: Revert to baseline PS requirement	Appropriate, as confirmed by the clinical expert consulted by CDR.
Separate survival curves for PS-independent (PS0) and PS-dependent (PS1-7) patients	Appropriate.
IFALD can develop in all PS-dependent patients	Appropriate.
Death rate assumed equal as to death rate PS-dependent patients	Appropriate.

CDR = CADTH Common Drug Review; IFALD = intestinal failure–related liver disease; PN = parenteral nutrition; PS = parenteral support; SOC = standard of care; STEPS = Study of Teduglutide Effectiveness in PS-Dependent Short Bowel Syndrome.

Manufacturer's Results

The incremental cost-utility ratio (ICUR) of teduglutide compared with SOC was reported by the manufacturer at $1,600,145 per QALY.

TABLE 9: INCREMENTAL COST-UTILITY RATIO OF TEDUGLUTIDE COMPARED WITH STANDARD OF CARE

	SOC	Teduglutide
Costs		
Drug cost	-	$2,771,149.45
Administration training	-	$35.90
Colonoscopy	-	$2,579.44
Parenteral support	$1,063,218.44	$706,551.75
IFALD	$121,041.70	$89,457.61
Adverse events	$43,240.26	$14,336.43
Total Costs	**$1,227,500.40**	**$3,584,110.57**
QALYS		
No PN	0.00	1.58
PN 1 day per week	0.00	0.13
PN 2 days per week	0.01	0.31
PN 3 days per week	0.46	0.53
PN 4 days per week	0.50	0.64
PN 5 days per week	0.22	0.20
PN 6 days per week	0.58	0.16
PN 7 days per week; < 28 L PN per week	1.34	1.00
PN 7 days per week; ≥ 28 L PN per week	0.13	0.00
IFALD utility decrement	0.90	0.72
Total QALYs	**2.35**	**3.82**
Incremental cost	-	**$2,356,610.91**
Incremental QALY	-	**1.47**
ICUR ($/QALY gained)	-	**$1,600,145.36**

ICUR = incremental cost-utility ratio; IFALD = intestinal failure–associated liver disease; PN = parenteral nutrition; QALY = quality-adjusted life-year; SOC = standard of care.
Source: Adapted from manufacturer's pharmacoeconomic submission. [1]

Manufacturer's sensitivity analyses

In addition to the base-case analyses, the manufacturer conducted probabilistic analyses and one-way sensitivity analyses to assess the uncertainty associated with the model parameters, inputs, and assumptions (Table 10). The results of the manufacturer's sensitivity analyses indicate that the model results are sensitive to the model time horizon, rates of IFALD, and other adverse events. The results were also sensitive to the selected survival curve used in the model.

TABLE 10: RESULTS OF MANUFACTURER'S SENSITIVITY ANALYSES

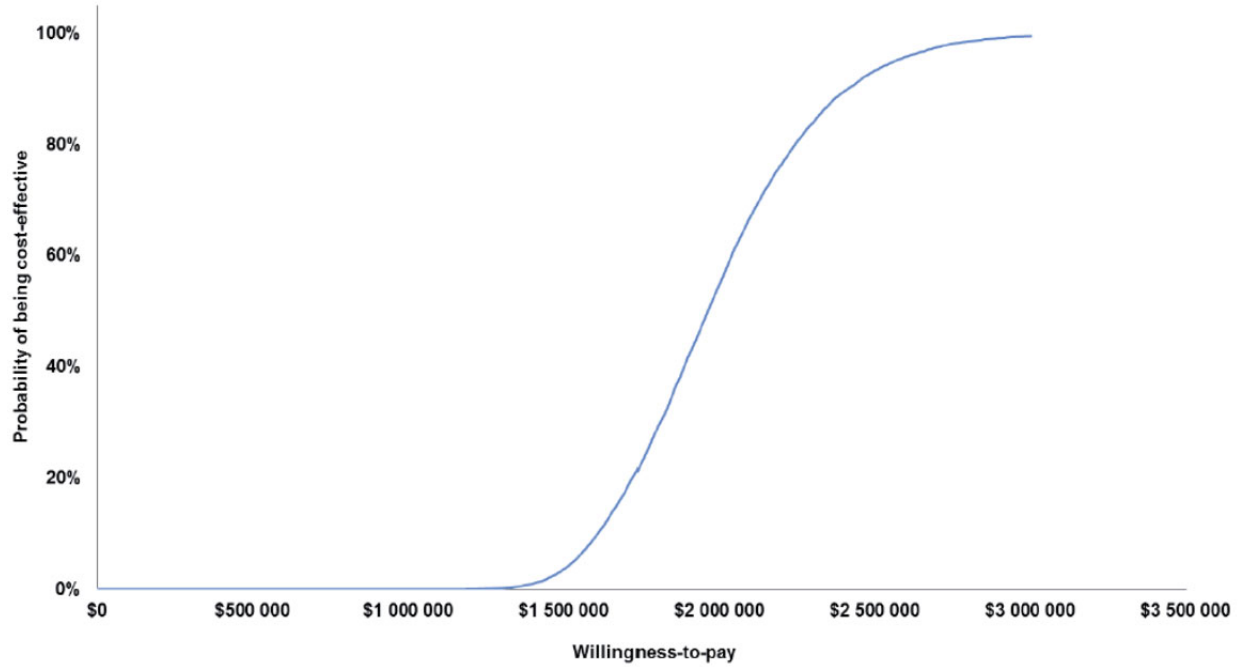
Base-Case Setting	Scenario Setting	ICUR ($/QALY)
Base-case model	-	1,600,145
Time horizon: 40 years	10 years 20 years 30 years 50 years	1,874,513 1,667,712 1,615,180 1,597,381
Discount rate: 5%	Discount rate: 3%	1,537,997
All AEs included	Only serious AEs	1,835,844
IFALD: included in model	IFALD: not included	1,844,973
Cost of PS: midpoint to the source range	Cost of PS: low Cost of PS: high	1,660,690 1,539,601
PS requirement maintained for teduglutide patients beyond 30 months	Last observed teduglutide transitions carried forward	1,418,515
SOC patients revert to baseline PS requirement beyond 24 weeks	PS requirement maintained for SOC patients beyond 24 weeks	1,971,815
Survival curve: log-normal	Exponential Gamma Gompertz Log-logistic Weibull	1,426,537 1,600,179 1,772,514 1,619,833 1,609,686

AE= adverse event; ICUR = incremental cost-utility ratio; IFALD = intestinal failure–associated liver disease; PS = parenteral support; QALY = quality-adjusted life-year; SOC = standard of care.
Source: Adapted from manufacturer pharmacoeconomic submission, Table 19 (page 44).[1]

Probabilistic sensitivity analysis

The manufacturer performed the probabilistic sensitivity analysis (PSA) by conducting 10,000 Monte Carlo simulations in which values of key parameters were drawn randomly and independently from the parameter distributions. Beta distributions were used for utilities and adverse events, whereas gamma distributions were used for costs. Transition probabilities were included in the PSA using a Dirichlet distribution, with an informed prior assumption that patients can either stay in their present PS state or move up or down by one state. The results of the manufacturer's PSA indicate that teduglutide has a 50% likelihood of being cost-effective compared with SOC only at a threshold of $1,960,000 per QALY gained.

FIGURE 2: COST-ACCEPTABILITY CURVE OF MANUFACTURER'S BASE-CASE ANALYSIS



Source: Manufacturer's pharmacoeconomic submission.[1]

CADTH Common Drug Review Reanalyses

Teduglutide stopping rule

Based on the STEPS clinical trials program, patients who did not experience at least a 20% PS reduction after 24 weeks would discontinue teduglutide and then receive PS only.[3] This stopping rule was confirmed appropriate by the clinical expert consulted by CDR but had not been included in the manufacturer's base case and sensitivity analyses. CDR conducted a scenario analysis that activated the stopping rule for teduglutide patients. The results are summarized in Table 11.

TABLE 11: SUMMARY RESULTS OF CADTH COMMON DRUG REVIEW REANALYSIS ON TEDUGLUTIDE STOPPING RULE

		Costs ($)	Incremental Costs ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
Stopping rule turned off (manufacturer base case)	SOC	1,227,500		2.35		
	TED	3,584,111	2,356,610	3.82	1.47	1,600,145
Stopping rule activated (CDR reanalysis)	SOC	1,227,500		2.35		
	TED	3,031,535	1,804,035	3.48	1.13	1,589,764

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care; TED = teduglutide.
Source: Adapted from manufacturer's pharmacoeconomic submission, Table 18 (page 42).[1]

Administration of parenteral support

The manufacturer's base-case model assumed that 50% of patients require nurse-led administration of PS, with the remaining 50% self-administering. This assumption was not justified by the manufacturer, nor was it confirmed correct by the clinical expert consulted by CDR — the appropriate proportions to be used are unknown. Therefore, as self-administration of PS incurs a lower cost than nurse-led administration, CDR conducted one-way sensitivity analyses varying the percentage of patients self-administering PS. The results are summarized in Table 12.

TABLE 12: SUMMARY RESULTS OF CADTH COMMON DRUG REVIEW REANALYSIS ON PS ADMINISTRATION

Percentage of Patients Self-Administering PS		Costs ($)	Incremental Costs ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
50% (base-case assumption)	SOC	1,227,500		2.35		
	TED	3,584,111	2,356,610	3.82	1.47	1,600,145
25%	SOC	1,279,225		2.35		
	TED	3,618,483	2,339,259	3.82	1.47	1,588,364
75%	SOC	1,175,776		2.35		
	TED	3,549,738	2,373,962	3.82	1.47	1,611,927

ICUR = incremental cost-utility ratio; PS = parenteral support; QALY = quality-adjusted life-year; SOC = standard of care; TED = teduglutide.
Source: Adapted from manufacturer pharmacoeconomic submission, Table 18 (page 42).[1]

PS health state utilities

Whereas there is uncertainty regarding the manufacturer's utility exercise, CDR considered reanalyses based on available information on utility values from the manufacturer's original exercise. The PS health state utility values were derived from the trend line resulting from fitting average utility data from a Web-survey. Fitting the values to develop the trend line revealed discrepancies that were not explained in the manufacturer's submitted report. As CDR was unable to identify any publicly available evidence on utility scores for SBS, a reanalysis was conducted using only utility values directly from the manufacturer's results of the Web-survey. As the reanalysis was based on the same utility data set, the results were, expectedly, not significantly impacted (Table 13). It should be emphasized that the cost-effectiveness analysis is associated with high uncertainty from the utility values used for PS health states.

TABLE 13: SUMMARY RESULTS OF CADTH COMMON DRUG REVIEW REANALYSIS ON HEALTH STATE UTILITIES

		Costs ($)	Incremental Costs ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
Utilities from trend line[a]	SOC	1,227,500		2.35		
	TED	3,584,111	2,356,610	3.82	1.47	1,600,145
Utilities from Web-survey	SOC	1,227,500		2.24		
	TED	3,584,111	2,356,610	3.70	1.46	1,609,766

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care; TED = teduglutide.
[a] Manufacturer's base-case assumption.
Source: Adapted from manufacturer's pharmacoeconomic submission, Table 18 (page 42).[1]

Utility associated with IFALD

The health state utility value associated with IFALD in the manufacturer's base-case model was derived from a UK-specific study that reported utility scores for general liver complications without a specific utility value for PS-related liver complications. CDR conducted a reanalysis using an alternate utility value for liver disease from a publication by Sullivan and Ghushchyan that also reflected general liver disorders.[12] Results are summarized in Table 14.

TABLE 14: SUMMARY RESULTS OF CADTH COMMON DRUG REVIEW REANALYSIS ON LIVER DISEASE UTILITIES

		Costs ($)	Incremental Costs ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
0.596[a]	SOC	1,227,500		2.35		
	TED	3,584,111	2,356,610	3.82	1.47	1,600,145
0.729[b]	SOC	1,227,500		2.64		
	TED	3,584,111	2,356,610	4.06	1.41	1,666,666

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; SOC = standard of care; TED = teduglutide.
[a] Manufacturer's base-case assumption.
[b] Based on US-based publication by Sullivan and Ghushchyan (2006).[12]
Source: Adapted from manufacturer's pharmacoeconomic submission, Table 18 (page 42).[1]

Multi-way sensitivity analysis

A multi-way sensitivity analysis was conducted to explore the impact of the variability between utility values directly derived from the Web-survey and utility values estimated from trend line on the teduglutide stopping rule. The results were not significantly different, therefore confirming the stopping rule as the key driver for the result differences.

Price reduction scenario

A price reduction analysis was conducted for the manufacturer's base-case analysis and for CDR's scenario analyses that varied the health state utilities and applied (or not) the stopping rule for teduglutide patients, when comparing teduglutide to SOC in patients with SBS (
Table 15).

TABLE 15: RESULTS OF PRICE REDUCTION SCENARIOS

ICURs of Submitted Drug Versus Comparator			
Reduction	Manufacturer Base Case ($/QALY)	CDR Scenario Analysis (With Stopping Rule) ($/QALY)	CDR Scenario Analysis (Without Stopping Rule) ($/QALY)
Submitted price[a]	1,600,145	1,607,126	1,607,766
25%	1,129,741	1,134,377	1,136,533
50%	659,336	661,627	663,300
75%	188,931	188,877	190,067
80%	94,850	94,327	95,421
81%	76,034	75,417	76,491
82%	57,218	56,507	57,562
83%	38,402	37,597	38,633
84%	19,586	18,687	19,703
85%	769	Teduglutide dominant[b]	774

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
[a] Manufacturer's submitted confidential price of $[redacted] per 5 mg vial.[1]
[b] A dominant option results in increased benefits at a lesser cost than the comparator.

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