CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

TELOTRISTAT ETHYL (XERMELO)

(Ipsen Biopharmaceuticals Canada Inc.)

Indication: Refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients inadequately controlled by SSA therapy alone

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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

BM	bowel movement
CDR	CADTH Common Drug Review
CS	carcinoid syndrome
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQol 5-Dimensions questionnaire
ICUR	incremental cost-utility ratio
NET	neuroendocrine tumour
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RFA	radiofrequency ablation
SSA	somatostatin analogue

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Telotristat ethyl (Xermelo) 250 mg
Study Question	Is telotristat ethyl, in combination with somatostatin analogues (SSAs), a cost-effective alternative to SSA monotherapy for the treatment of patients with refractory carcinoid syndrome diarrhea that is inadequately controlled by SSA therapy alone?
Type of Economic Evaluation	Cost-utility analysis (CUA)
Target Population	Patients with refractory carcinoid syndrome diarrhea that is inadequately controlled by SSA therapy alone
Treatment	Telotristat ethyl in combination with SSA
Outcome	Quality-adjusted life-years (QALYs)
Comparator	SSA monotherapy
Perspective	Canadian public health care payer
Time Horizon	30 years
Results for Base Case	• Telotristat ethyl in combination with SSAs was associated with an incremental cost-utility ratio (ICUR) of $836,293 in the revised base case. • The ICUR was found to be below $50,000 per QALY in 0% of simulations.
Key Limitations	• The manufacturer defined model states in terms of remaining on or discontinuing treatment (based on the response to treatment in the initial phase), rather than in terms of the health states experienced by the patient. Using this modelling approach, it is not possible to establish what is causing differences in utility values between treatment groups. The use of treatment-specific utilities is not in line with CADTH's economic evaluation guidelines. • The utility values used by the manufacturer in the economic model are not based on the TELESTAR trial but sourced from a published quality-of-life study that asked the general public to value the health states of patients with neuroendocrine tumours. This study defined health states in terms of EQ-5D domains. It is unclear how health states in this valuation study relate to the model's health states that are defined in terms of treatment continuation or discontinuation based on change in frequency of bowel movements. Moreover, there is a larger difference (i.e., 0.171) in utility values between treatment responders and nonresponders in the valuation study compared with the observed utility difference in the TELESTAR trial (i.e., 0.073); this favours telotristat ethyl. Furthermore, the TELESTAR trial did not find any statistically significant improvement in overall quality of life between treatment groups. The trial findings do not correspond to the findings of the economic model, suggesting the model overestimated the clinical benefits associated with telotristat ethyl. • The long-term validity of model parameters and assumptions, particularly those related to efficacy, survival, and subsequent therapy, are uncertain, as they are based on short-term trial evidence that was extrapolated to a 30-year time horizon.
CDR Estimate(s)	The CDR base-case analysis used utility values based on the TELESTAR trial. It found that the ICUR for telotristat and SSA combination therapy was $1.96 million per QALY when compared with SSA monotherapy. Based on this estimate, a price reduction of at least 95% would be required for telotristat ethyl to achieve an ICUR of less than $100,000 per QALY and more than 97.5% for an ICUR of less than $50,000 per QALY. In the CDR scenario analyses, reducing the time horizon to one year increased the ICUR to $3.39 million per QALY for telotristat and SSA, and including a subsequent therapy after treatment failure increased the ICUR to $28.07 million per QALY, illustrating considerable uncertainty in the base case.

CDR = CADTH Common Drug Review; EQ-5D = EuroQol 5-Dimensions questionnaire; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; SSA = somatostatin analogue.

Drug	Telotristat ethyl (Xermelo)
Indication	Indicated for the treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients inadequately controlled by SSA therapy alone.
Reimbursement Request	As per indication.
Dosage Form	Tablets
NOC Date	October 12, 2018
Manufacturer	Ipsen Biopharmaceuticals Canada Inc.

Executive Summary

Background

Telotristat ethyl (Xermelo) is a tryptophan hydrolase inhibitor indicated for the treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients whose condition is inadequately controlled by SSA therapy alone.[1] Carcinoid syndrome occurs in patients with neuroendocrine tumour (NET).[2] The manufacturer's submission reports that, in Canada, approximately 0.45 per 100,000 people may have carcinoid syndrome diarrhea inadequately controlled with first-line SSA therapies. Telotristat ethyl is available as a 250 mg oral tablet to be taken three times daily and is priced at $84.82 per tablet.[3]

The manufacturer submitted a cost-utility analysis of telotristat in combination with SSA therapy compared with SSA monotherapy over a 30-year time horizon.[3] The perspective was that of a Canadian public health care payer, with a discount rate of 1.5% applied to costs and benefits accrued after the first year. Patients showing durable response to treatment over the first 12 weeks, defined as a ≥ 30% reduction in bowel movement (BM) frequency for ≥ 50% of the 12-week period (note: patients in the pivotal TELESTAR trial had on average 5 to 6 BMs per day at baseline), were assumed to continue on the treatment until treatment discontinuation or death. Those who did not show a durable response were assumed to continue on SSA monotherapy until death, i.e., no subsequent therapy was included. In the manufacturer's base case, other subsequent therapies for NET were not assumed to be available after treatment failure, but were evaluated in a scenario analysis. The manufacturer incorporated patient characteristics and efficacy parameters based on the phase III TELESTAR trial, which compared telotristat in combination with SSA therapy with SSA monotherapy in patients with refractory carcinoid syndrome diarrhea that is inadequately controlled by SSA monotherapy. Transition to death was based on the survival analysis of a phase III CLARINET trial that compared lanreotide autogel with placebo in those with enteropancreatic NET. Health-state utilities were based on a published valuation study conducted in the general UK population, and costs were derived from the Ontario Drug Benefit Formulary, the Ontario Case Costing Initiative, and the Ontario Schedule of Benefits and Fees.

The manufacturer reported that telotristat in combination with SSA therapy was associated with higher costs and quality-adjusted life-years (QALYs) than SSA monotherapy, resulting in an incremental cost-utility ratio (ICUR) of $836,293 per QALY in the manufacturer's base case (note: the manufacturer's original submission reported an ICUR of $846,693, which

was revised after correcting minor programming errors). The manufacturer also undertook scenario analyses that explored the impact of different time horizons, survival duration, time to response, and subsequent therapies. Among these scenarios, including a subsequent therapy with 100% response rate had the greatest impact; the resulting ICUR was between $5.7 million and $13.1 million per QALY, depending on the cost of subsequent therapy.

Summary of Identified Limitations and Key Results

CDR identified a number of key limitations of the model submitted by the manufacturer. Firstly, the manufacturer defined model states beyond the initial 12-week period, in terms of staying on or discontinuing treatment, rather than the health states experienced by the patient with refractory carcinoid syndrome diarrhea. Using this modelling approach, it is not possible to establish what is causing the differences in utility values between treatment groups. The use of treatment-specific utilities is discouraged, as the more transparent approach is to assign utility values to clinically relevant health states, as per CADTH economic evaluation guidelines.[4]

Secondly, the manufacturer reported that treatment responders had, counterintuitively, lower utility than nonresponders in the TELESTAR trial.[5] As such, the utility values in the economic model (for both decision-tree and Markov model parts) were instead based on a health-state valuation study from the literature.[6] The valuation study defined stable NET disease solely in terms of the EuroQol 5-Dimensions questionnaire (EQ-5D) domains (without specifying BM frequency). The resulting utility values were used in the economic model as estimates of utility values of treatment response. It is unclear how the valuation study health-state relates to the modelled states, which are solely defined in terms of treatment continuation or discontinuation based on changes in BM frequency (i.e., discontinue unless ≥ 30% reduction in BM frequency during ≥ 50% of the 12-week follow-up period). Moreover, the BM frequency in nonresponders was assumed to be equivalent to patients with grade 3 or 4 diarrhea (i.e., at least 7 BMs per day over baseline, as defined in the valuation study), which is greater than the frequency observed in the TELESTAR trial (i.e., 5 to 6 BMs per day). As a result, based on the valuation study, there is a greater difference (i.e., 0.171) in utility values between treatment responders and nonresponders than the difference observed between these groups in the TELESTAR trial (i.e., 0.073); this favours telotristat ethyl. Furthermore, TELESTAR trial did not find any statistically significant improvement in overall quality of life between treatment groups; this is not reflected in the economic model.

Finally, key efficacy and safety parameters were based on short-term evidence and extrapolated over a 30-year time horizon. The validity of these parameter estimates over the longer term is uncertain. The ICUR was observed to be especially sensitive to assumptions regarding subsequent therapies after treatment failure, for which there is substantial uncertainty.

The CADTH Common Drug Review (CDR) base case addressed the key limitation related to quality-of-life data in the economic model by using health-state utility values from the manufacturer's utility analysis of TELESTAR trial.[7] Based on this, the utility values for "remain on treatment" and "discontinue treatment" health states were estimated using the baseline utility plus the change in utility over the 12-week follow-up in the TELESTAR trial. In the CDR base case, the ICUR for telotristat in combination with SSA versus SSA monotherapy was $1.96 million per QALY. Based on this estimate, a price reduction of at least 95% would be required for telotristat ethyl to achieve an ICUR of less than $100,000

per QALY, and more than 97.5% for an ICUR of less than $50,000 per QALY. CDR undertook scenario analyses to explore the potential impact of different time horizons and subsequent therapy assumptions on cost-effectiveness results. Shortening the time horizon to 10 years and one year increased the ICUR to $1.98 million and $3.39 million per QALY, respectively. This shows that using a longer time horizon, based on uncertain evidence, favours telotristat. The ICUR was also sensitive to the assumption of subsequent therapy for patients whose condition failed to respond to the initial treatment (either SSA combination therapy or monotherapy); the ICUR in this scenario increased to $28.07 million per QALY.

Conclusions

A key limitation of the model submitted by the manufacturer was the incorporation of utility values that were not consistent with the health-related quality-of-life results of the TELESTAR trial. CDR was able to address this limitation by deriving utility values from the manufacturer's utility analysis of the TELESTAR trial. In the CDR base case, the ICUR for telotristat and SSA combination therapy was significantly higher than the manufacturer's estimate of $1.96 million per QALY. Based on the CDR base case, a price reduction of at least 95% would be required for telotristat ethyl to achieve an ICUR of less than $100,000 per QALY, and more than 97.5% for an ICUR of less than $50,000 per QALY.

There is significant uncertainty associated with the estimated cost-effectiveness of telotristat ethyl due to uncertain long-term effects of treatment and subsequent therapies. In the CDR reanalysis, reducing the time horizon to one year increased the ICUR to $3.39 million per QALY, and including a subsequent therapy after treatment failure (in the base case) increased the ICUR to $28.07 million per QALY for telotristat and SSA, illustrating the impact of the considerable uncertainty.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis that compared telotristat in combination with somatostatin analogue (SSA) therapy versus SSA monotherapy in adult patients with refractory carcinoid syndrome diarrhea that is inadequately managed on SSA monotherapy alone.[5] The analysis was probabilistic and conducted from a Canadian public health care payer perspective. The model structure consisted of an initial 12-week decision-tree and a lifetime (30-year) Markov state–transition model. The initial decision tree divided patients into two response categories: those who experience durable response, defined as ≥ 30% reduction in bowel movement (BM) frequency for ≥ 50% of the 12-week period of the trial, and those who do not experience durable response.

Patients then continued into a Markov state–transition model with the following health states: "remain on treatment," "discontinue treatment" due to adverse events or lack of efficacy, or "death." All patients were assumed to receive SSA until death. Subsequent therapies such as everolimus, interferon-alfa, peptide receptor radionuclide therapy (PRRT) and radiofrequency ablation (RFA) were not modelled in the manufacturer's base-case analysis; however, these therapies were explored in scenario analyses (Table 14) and were assumed to elicit durable response in all patients. Carcinoid disease progression was also not modelled in the analysis.

Patient characteristics, efficacy, and discontinuation parameters were informed by the manufacturer-conducted phase III TELESTAR trial,[5] which was a 12-week double-blinded trial followed by a 36-week open-label extension comparing telotristat in combination with SSA therapy with placebo in combination with SSA therapy.[8] The transition probability to death was based on the manufacturer's conducted survival analysis of the six-year CLARINET trial (that compared lanreotide with placebo in a population with metastatic enteropancreatic neuroendocrine tumour [NET]). The utility values associated with health states were informed by a valuation study conducted in the general UK population.[6] This valuation study estimated the utility value for stable NET health-state (defined in terms of the EuroQol 5-Dimensions questionnaire [EQ-5D] domains, without adverse events) to be 0.771; this was assigned to "remain on treatment" state in the model. Then, the utility value estimated in the valuation study for stable disease with diarrhea (0.600) was assigned to "discontinue treatment" state. Adverse events were not explicitly modelled in the base case, although key adverse events found in the manufacturer's targeted literature search were included for subsequent therapies only in scenario analyses. Costs of drugs, procedures, and patient monitoring were sourced from Ontario formulary, case costing, and the Schedule of Benefits and Fees, where available.[5] Remaining cost and resource use data gaps were supplemented through a targeted literature search and clinician opinion. A number of additional model parameters and assumptions regarding SSA dose, mortality, and subsequent therapies were reported as being based on discussions with Canadian clinicians.

Manufacturer's Base Case

The CADTH Common Drug Review (CDR) identified the following discrepancies between the submitted pharmacoeconomic model and pharmacoeconomic report, which were corrected: the baseline SSA doses were corrected in the economic model to be the same for the telotristat plus SSA combination therapy group and the SSA monotherapy group (this is consistent with the pharmacoeconomic report). In addition, the manufacturer has clarified that the pharmacy dispensing fee for a 30-day supply ($8.83 per prescription in Ontario)[9] was incorrectly costed at $9.93.[7] Both input parameters were corrected in the revised manufacturer's base case (Table 2). The results of the original manufacturer's base case are available in Table 13.

The revised manufacturer base case estimated a probabilistic incremental cost-utility ratio (ICUR) of $836,293 per quality-adjusted life-year (QALY) gained for telotristat in combination with SSA therapy compared with SSA monotherapy. At a willingness-to-pay threshold of $50,000 per QALY, the probability of the telotristat and SSA combination therapy being cost-effective compared with SSA monotherapy was 0%.

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

Comparator	Total Cost ($)	Incremental Cost ($)	Total QALYs	Incremental QALYs	ICUR ($ per QALY Gained)
SSA	293,680	–	5.079	–	–
Telotristat ethyl, in combination with SSA	425,581	131,902	5.236	0.158	836,293

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years; SSA = somatostatin analogue.

Summary of Manufacturer's Sensitivity Analyses

Of the scenario analyses submitted by the manufacturer (Table 14), the pharmacoeconomic model results were found to be most sensitive to assumptions regarding subsequent therapy and treatment response. An increasing proportion of patients responding to the telotristat and SSA combination therapy, from 42.3% observed in the TELESTAR trial to 98%, resulted in a reduced incremental cost ($280,001) and increased incremental QALYs (0.435), reducing the ICUR for the telotristat and SSA combination therapy to $644,191 per QALY. In contrast, assuming the administration of a subsequent therapy after treatment failure with SSA or combination therapy resulted in significantly larger ICURs that ranged from $5.7 million to $13.1 million per QALY gained, depending on the subsequent therapy (and the associated cost) assumed in the scenario analysis. This was mainly driven by the assumption that all patients were assumed to respond to the subsequent therapy. The QALY difference between treatment groups is significantly reduced in these scenarios because patients who do not respond to SSA monotherapy or combined therapy eventually respond to subsequent therapy; thereby reducing the incremental QALY difference.

Limitations of Manufacturer's Submission

The following limitations were identified with the manufacturer's pharmacoeconomic submission:

- **Markov model structure was based on treatment rather than health states**: The manufacturer defined the states in the Markov part of the model (week 12 to 30 years) in terms of remaining on or discontinuing treatment, rather than on the health states experienced by the patient with refractory carcinoid syndrome diarrhea. Using this modelling approach, it is not possible to establish what is causing differences in utility values between treatment groups and may allow the difference to be driven by factors that are not clinically relevant. The use of treatment-specific utilities is discouraged, as the more transparent approach is to assign utility values to clinically relevant health states, as per CADTH's economic evaluation guidelines.[4]
- **Utility values used in the model do not reflect the quality-of-life evidence in the clinical trial:** The manufacturer reported that treatment responders had, counterintuitively, lower utility than nonresponders in the TELESTAR trial.[5] Therefore, health utility values in the economic model were based on a health-state valuation study from the literature[6] and not based on the utility values from the TELESTAR trial. The published valuation study defined the "stable disease" NET health state in terms of the EQ-5D domains (with no indication of the number of BMs); this was assumed to be equivalent to the "remain on treatment" health state in patients who experienced durable response (defined primarily in terms of BMs).[10] It is unclear whether these health states can be assumed to be equivalent. Also, the utility value for the "discontinue treatment" health state in the economic model was assumed to be equivalent to the stable disease NET with grade 3 or 4 diarrhea, as defined in the same health-state valuation study. This is also uncertain, as grade 3 or 4 diarrhea is typically defined as at least seven BMs per day over baseline,[11] which is inconsistent with the mean baseline frequency of five to six BMs per day experienced by the patients in the TELESTAR trial.[10] Moreover, the difference in utility values between "remain on treatment" and "discontinue treatment" health states (when utility values were based on the valuation study) was significantly larger (i.e., 0.171) than the utility difference observed between the durable response and non-response groups in the TELESTAR trial (0.073 based on the manufacturer's utility analysis[7]). Finally, the clinical trial did not find any statistically significant difference in the overall quality of life (based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC-QLQ-C30] global health scale) between treatment groups, and in most other health-related quality-of-life outcomes. For the two subscales of EORTC-QLQ-C30 that reported statistically significant differences (i.e., diarrhea and insomnia), the CDR clinical report could not draw a clear conclusion, as these were not adjusted for multiple comparisons. In summary, using health utility values from the valuation study (as opposed to the clinical trial) increased the health utility benefit attributable to telotristat ethyl.
- **Uncertain long-term validity of model parameters and assumptions:** The manufacturer's submission was based on the assumption that the short-term evidence obtained from the clinical trial can be extrapolated to a 30-year time horizon; this assumption introduces significant uncertainty in the analysis. It is unclear for example, whether the probability of drug discontinuation (whether due to adverse events or lack of efficacy) observed over the short term (i.e., 36 weeks for telotristat and SSA combination therapy and 12 weeks for SSA monotherapy) would remain the same over a 30-year time horizon (as assumed in the economic model). Another model parameter, overall survival, was projected over a 30-year time horizon based on six-year data. Further uncertainty is contributed by lack of clear treatment sequencing after treatment failure, supported by current clinical guidelines or clinical opinion. The manufacturer's scenario analysis clearly demonstrates the potentially significant impact of different treatment sequencing assumptions on ICURs.

Additional limitations or areas of concern were noted in Table 11 and Table 12.

CADTH Common Drug Review Reanalysis

CDR conducted a reanalysis that addressed the limitation with the utility data used in the manufacturer's economic analysis. Instead of using the UK health-state valuation study, CDR used utility values derived from the manufacturer's utility analysis of the EORTC data from the TELESTAR trial.[7] The utility value for treatment responders who experienced the "remain on treatment" health state was obtained as the sum of baseline utility score (0.522) and 12-week change score (i.e., 0.074 for treatment responders). Similarly, the utility value for the "discontinue treatment" health state was the sum of baseline utility and the change score for nonresponders (0.001) observed in the TELESTAR trial (Table 3).

Table 3: Health-State Utility Parameters for the CDR Reanalysis

Parameter	Manufacturer's Base Case[a]	CDR Base Case[b]
"Remain on treatment" health-state utility (i.e., patients with durable response)	0.771	0.522 + 0.074 = 0.596
"Discontinue treatment" health-state utility (i.e., patients without durable response)	0.600	0.522 + 0.001 = 0.523

CDR = CADTH Common Drug Review; EORTC = European Organization for Research and Treatment; NET = neuroendocrine tumour.

[a] The parameters for the manufacturer's base case were extracted from a NET health-state valuation study.[6]

[b] The parameters for CDR reanalysis were based on the manufacturer's utility analysis of the EORTC data from TELESTAR trial.[7] The mean utility value for CDR base case was calculated as a sum of baseline utility score (0.522) and a 12-week change score (i.e., 0.074 for patients with durable response and 0.001 for patients without durable response). THE SD and n parameters were based on the data available for the 12-week change score analysis.

The ICUR in the CDR base-case analysis was $1.96 million per QALY for telotristat in combination with SSA therapy compared with SSA monotherapy (Table 4). At a threshold of $50,000 per QALY, none of the 5,000 probabilistic simulations reported the telotristat and SSA combination therapy as a cost-effective intervention.

In addition, scenario analyses were conducted to explore the uncertainty associated with key model assumptions (Table 4):

- **10-year time horizon:** A short 10-year time horizon was explored to reduce the uncertainty associated with extending model parameters and assumptions over a longer 30-year time horizon.
- **One-year time horizon**: A shorter one-year time horizon was also explored that approximates the duration of the TELESTAR study (12-week double-blind treatment period followed by a 36-week open-label extension period).[8]
- **Subsequent therapy added for patients whose condition did not respond to SSA or SSA and telotristat therapy:** As the manufacturer's scenario analyses demonstrated the significant impact that considerations on subsequent therapies had on the ICUR, this was also explored in the CDR scenario analysis. The following subsequent therapies were included based on their respective market shares, as informed by the clinicians the manufacturer interviewed for the submission: de-bulking surgery = 7%, everolimus = 20%, interferon-alfa = 2%, PRRT = 21%, RFA = 7%, selective internal radiation therapy [SIRT] = 7%, transcatheter arterial chemoembolization [TACE] = 5%, transarterial embolization [TAE] = 33%).[5]

The time horizon scenario analyses found that the ICUR values increased with a shorter time horizon (i.e., $1.98 million per QALY for a 10-year time horizon and $3.39 million per

QALY for a one-year time horizon), indicating that a longer time horizon favours telotristat. Given the uncertainty associated with extending model parameters and the assumptions associated with efficacy, survival, and treatment sequence over the long-term, it is uncertain whether a longer duration of telotristat treatment up to 30 years could be expected in clinical practice. In the scenario analysis that included subsequent therapies after treatment failure, the ICUR increased to more than $28.07 million per QALY.

Table 4: CDR Reanalysis (Versus Somatostatin Analogue Monotherapy)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY Gained)
	Revised manufacturer's base case	Telotristat ethyl in combination with SSA	425,581	5.236	–
		SSA	293,680	5.079	–
		Incremental	131,902	0.158	836,293
	CDR base case	Telotristat ethyl in combination with SSA	426,999	4.486	–
		SSA	294,779	4.418	–
		Incremental	132,220	0.067	1,961,202
Scenario Analyses					
1	10-year time horizon	Telotristat ethyl in combination with SSA	364,404	3.590	–
		SSA	234,821	3.524	–
		Incremental	129,583	0.066	1,979,078
2	One-year time horizon	Telotristat ethyl in combination with SSA	82,450	0.538	–
		SSA	34,429	0.524	–
		Incremental	48,021	0.014	3,389,489
3	Subsequent therapy based on the average clinician opinion reported by the manufacturer	Telotristat ethyl in combination with SSA	556,311	4.974	–
		SSA	441,449	4.970	–
		Incremental	114,862	0.004	28,067,239

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years; SSA = somatostatin analogue.

CDR conducted further analyses to establish the price reduction at which the ICUR of telotristat in combination with SSA therapy would be less than $100,000 per QALY (Table 5).

Table 5: CDR Reanalysis Price-Reduction Scenarios

ICURs of Telotristat and SSA Combination Therapy Versus SSA Monotherapy		
Price	**Revised Manufacturer's Base-Case Analysis[a]**	**CDR Base Case**
Submitted	$836,293 per QALY	$1,961,202 per QALY
85% reduction	$125,914 per QALY	$296,118 per QALY
90% reduction	$84,744 per QALY	$200,131 per QALY
95% reduction	$42,713 per QALY	$99,500 per QALY
97.5% reduction	$21,886 per QALY	$51,130 per QALY
98% reduction	$17,663 per QALY	$41,635 per QALY

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SSA = somatostatin analogue.

[a] Revised from the manufacturer's base-case analysis, as reported in Table 2.

Patient Input

Patient input gathered by Carcinoid Neuroendocrine Tumour Society (CNETS) Canada was obtained from an online survey of a caregiver and 10 NET patients who had experience with telotristat ethyl. The patients reported that diarrhea had the largest impact on patients' quality of life, followed by fatigue, flushing, abdominal pain, anxiety, and other symptoms of carcinoid syndrome. The multifactorial nature of the health-related quality of life reported by these patients suggests there are other aspects of carcinoid syndrome that are not addressed by telotristat and that may help explain the finding that there was no statistically significant difference for the EORTC-QLQ-C30 global health status scale between the treatment groups in the TELESTAR trial.[10]

Conclusions

A key limitation of the model submitted by the manufacturer was the incorporation of utility values that were not consistent with the health-related quality-of-life results of the TELESTAR trial. CDR was able to address this limitation by deriving utility values from the manufacturer's utility analysis of the TELESTAR trial. In the CDR base case, the ICUR for telotristat and SSA combination therapy was significantly higher than the manufacturer's estimate at $1.96 million per QALY. Based on the CDR base case, a price reduction of at least 95% would be required for telotristat ethyl to achieve an ICUR of less than $100,000 per QALY, and more than 97.5% for ICUR less than $50,000 per QALY.

There is significant uncertainty associated with the estimated cost-effectiveness of telotristat ethyl due to the uncertain long-term effects of treatment and subsequent therapies. In the CDR reanalysis, reducing the time horizon to one year increased the ICUR to $3.39 million per QALY, and including a subsequent therapy after treatment failure (in the base case) increased the ICUR to $28.07 million per QALY for telotristat and SSA, illustrating the impact of the considerable uncertainty.

Appendix 1: Cost Comparison

The comparators presented in Table 6 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 6: CDR Cost Comparison of Treatments for Adults With Refractory Carcinoid Syndrome Diarrhea That Is Inadequately Controlled by Somatostatin Analogue Monotherapy

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Telotristat ethyl (Xermelo)	250 mg	Tablet	84.8200[a]	250 mg orally three times a day	92,199
Standard-dose SSA					
Octreotide acetate (Sandostatin LAR)	30 mg	Injectable suspension	2,189.5200	30 mg intragluteal injection once every four weeks	28,464 (13 injections)
Lanreotide (Somatuline Autogel)	120 mg / 0.5 mL	Solution for injection	2,135.0500	120 mg deep subcutaneous injection in superior external quadrant of the buttock once every four weeks	27,756 (13 injections)
Increased-dose SSA					
Octreotide acetate (Sandostatin LAR)	30 mg	Injectable suspension	2,189.5200	60 mg intragluteal injection once every four weeks[b]	56,928 (26 injections)

CDR = CADTH Common Drug Review; LAR = long-acting release; SSA = somatostatin analogue.

All prices are from the Ontario Drug Benefit Formulary (accessed August 2018)[12] unless otherwise indicated and do not include the costs of product dispensing, dose preparation, or administration. Annual period assumes 52 weeks, or 13 × 4 weeks per year (365 days for all comparators). The calculated annual doses are based on product monograph where available and reported as a range of discrete number of doses if the calculated average dose is not a whole number. When multiple formulations were available, the least expensive type was used to calculate costs.

[a] Manufacturer submitted price.[3]

[b] Dosing based on clinical expert feedback and Al-Efraij et al. 2015 study.[13] Standard octreotide LAR is doubled.

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Telotristat in Combination With SSA Therapy Relative to the SSA Monotherapy?

SSA and Telotristat Ethyl Versus SSA Monotherapy	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
ICUR	$836,293 per QALY (revised manufacturer's base case) $1,961,202 per QALY (CDR base case)					

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; N/A = not applicable; QALY = quality-adjusted life-year; SSA = somatostatin analogue.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	The manufacturer clarified errors in reports and unclear methodology identified by CDR.		
Was the material included (content) sufficient?			X
Comments	Although the manufacturer corrected errors in the pharmacoeconomic model identified by CDR, the updated model was configured differently than the base case described in the report.		
Was the submission well organized and was information easy to locate?			X
Comments	There were spelling mistakes, erroneous references, and a missing scenario analysis result in both the original submission report and the updated report.		

CDR = CADTH Common Drug Review.

Table 9: 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

CDR = CADTH Common Drug Review.

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

The cost-effectiveness of telotristat for the treatment of patients with refractory carcinoid syndrome diarrhea that is inadequately controlled by somatostatin analogue (SSA) monotherapy has been assessed by Scottish Medicines Consortium (SMC)[14] and All Wales Medicines Strategy Group (AWMSG).[15,16] SMC and AWMSG reviews are summarized in Table 10.

Table 10: Health Technology Assessment Findings by the Scottish Medicines Consortium and All Wales Medicines Strategy Group

	SMC (June 2018)[14]	AWMSG (June 2018)[15,16]
Treatment	Telotristat ethyl (Xermelo) 250 mg film-coated tablets	
Price	£13,589 per year (1.00 GBP = 1.74 C$; June 2018).[17]	Redacted.
Similarities with CDR submission	• CUA compared telotristat + SSA versus SSA. • Hybrid model 30-year time horizon: initial 12-week decision-tree followed by a Markov cohort state–transition model with weekly transitions between response, non-response, and death states. • Patient characteristics, treatment efficacy, and discontinuation informed by TELESTAR trial. • Overall survival informed by manufacturer's survival analysis of CLARINET trial. • Time to initial response set to 6 weeks. • Utility value of stable disease NET with grade 3 or grade 4 diarrhea from Swinburn (2012).	
Differences with CDR submission	• Included PAS for telotristat. • Weighted average for subsequent treatment modelled for patients who discontinue. • Incorporated NHS reference costs. • Utility value minus patients in responder group who remain on treatment = 0.71. • Assumptions and generalizability of the study results verified by Scottish experts.	• Included PAS for telotristat. • Weighted average for subsequent treatment modelled for patients who discontinue. • Incorporated MIMS and NHS reference costs. • 70% of SC injections administered by nurse, 30% self-administered. • Monitoring resource uses a lower frequency for responders versus nonresponders (i.e., consultant-led monitoring every 6 months versus every 4 weeks). • Assumptions and generalizability of the study verified by Welsh experts.
Manufacturer's results	• Telotristat + SSA was dominant	• Telotristat + SSA was dominant compared with SSA in 71% of simulations if WTP = £20,000 or £30,000 per QALY.
Issues noted by the review group	• Cost savings dependent on highly uncertain assumptions on use of subsequent treatment. • Cost savings highly sensitive to discontinuation and response rates based on short-term data. • Uncertainty due to extrapolated mortality rate. • Utility difference response versus non-response group may be overestimated, as utility value represents health state without diarrhea instead of a reduction in BMs.	• Utility values from different patient population. • Utility values for responder group represent health state absent of diarrhea versus BMs. • Many model parameters and assumptions informed by one Welsh clinician. • Long-term discontinuation and response based on short-term trial with open-label period. • Lack of evidence for assumptions for subsequent treatment: overestimating efficacy of subsequent treatment and QALY for SSA, underestimating cost of subsequent treatment. • SAEs in TELESTAR and clinical expert consultation not modelled.
Results of reanalyses by review group	• None reported.	• None reported.

	SMC (June 2018)[14]	AWMSG (June 2018)[15,16]
Recommendation	SMC accepted telotristat for restricted use. Greater uncertainty was accepted as telotristat is indicated for an ultra-orphan condition.	AWMC recommended telotristat for restricted use, for treatment of CS diarrhea in adults that is inadequately controlled by SSA and who experience ≥ 4 BMs/day.

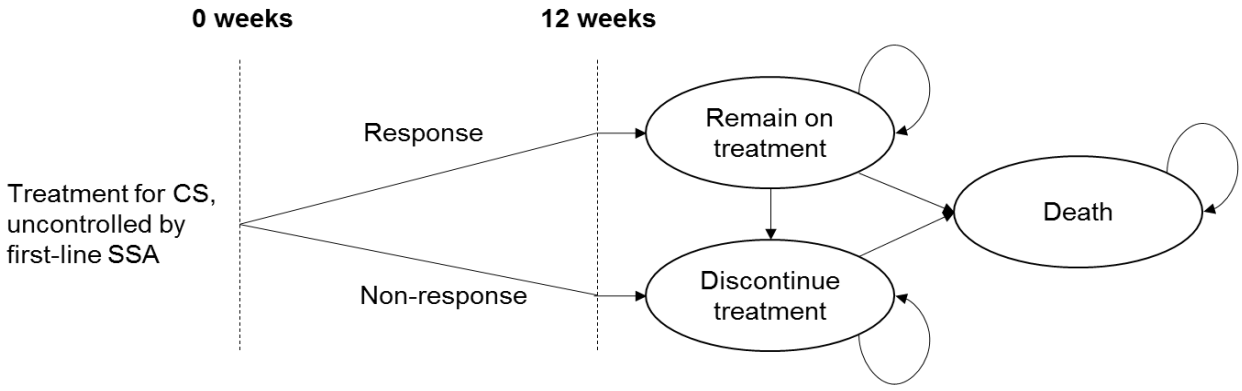
AWMSG = All Wales Medicines Strategy Group; BM = bowel movement; C$ = Canadian dollars; CDR = CADTH Common Drug Review; CS = carcinoid syndrome; CUA = cost-utility analysis; GBP = British pound sterling; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; MIMS = Monthly Index of Medical Specialities; NET = neuroendocrine tumour; NHS = National Health Service; PAS = patient access scheme; SAE = serious adverse event; SC = subcutaneous; SMC = Scottish Medicines Consortium; SSA = somatostatin analogue; WTP = willingness to pay.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis that was adapted for the Canadian setting from a global model developed for Scotland.[3] The probabilistic analysis modelled costs and the quality-adjusted life-years (QALYs) accrued to a cohort of adults with somatostatin analogue (SSA) monotherapy-refractory carcinoid syndrome with diarrhea over their lifetime from a Canadian public health care payer perspective. The model compared patients who received telotristat in combination with SSA therapy with patients who received SSA monotherapy and was structured as a hybrid of decision-tree and Markov state–transition models (Figure 1). An initial 12-week response-determination period was modelled using a decision tree; by the end of this period, patients were assumed to either achieve or fail to achieve a durable response, defined as "≥ 30% reduction in [bowel movement] BM frequency for ≥ 50% of [a 12-week] study period,"[8] and accrued costs and QALYs accordingly. Patients who experienced a durable response started in the "remain on treatment" health state in the proceeding Markov process and could transition to "discontinue treatment" or "death" states. Patients who did not experience durable response in the preceding decision tree started instead in the "discontinue treatment" state, where patients received SSA monotherapy (if patients received SSA monotherapy initially, they remained on SSA monotherapy despite the name of the health state) until death. The probability of response and discontinuation were based on the manufacturer's TELESTAR trial, and health utility values assigned to "remain on treatment" and "discontinue treatment" states were sourced from health-state preferences elicited from the UK general public and reflect "stable disease [neuroendocrine tumour] NET," and "stable disease NET with grade 3 or 4 diarrhea" states in patients with NET.[6] Except for diarrhea, adverse events were not modelled in the base-case analysis.

Figure 1: Manufacturer's Model Structure



CS = carcinoid syndrome; SSA = somatostatin analogue.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	The age, sex, and baseline SSA dose distribution of the modelled population were based on the TELESTAR phase III trial.	Appropriate.
Subsequent therapy	Two Canadian clinicians were consulted to inform the resource use and market share of subsequent therapies after discontinuation of telotristat and SSA combination therapy or SSA monotherapy for a scenario analyses.[5]	Acceptable. However, according to the clinical expert consulted by CDR, there is substantial uncertainty regarding subsequent therapy because of variation in access.
Efficacy	Response probabilities for telotristat and SSA combination therapy and SSA monotherapy were based on the 12-week result of the TELESTAR trial.	Appropriate.
Natural history	Natural history of NET and CS progression were not modelled.	Not applicable.
Discontinuations	Probability of discontinuation due to lack of response or adverse event for telotristat and SSA combination therapy were sourced from the 36-week open-label extension period of the TELESTAR trial. The corresponding parameter for SSA monotherapy was sourced from the 12-week double-blind trial period from the same trial.	Uncertain. It is unclear whether the discontinuation rate observed in the first 48 weeks of TELESTAR would continue over 30 years, i.e., the modelled time horizon.
Utilities	Utility values for the "remain on treatment" and "discontinue treatment" health states were sourced from a UK study[6] that elicited utility values of various NET health states. AE disutilities for the subsequent treatment-scenario analyses were sourced from a variety of studies focusing on adverse events found in	Inappropriate. It is uncertain how the "stable disease" NET health state without grade 3 or 4 diarrhea relates to the "remain on treatment" health state representing patients with durable response, defined as a ≥ 30% reduction in BM frequency during ≥ 50% of the 12-week double-blind trial period. Also, the utility value assigned to "discontinue treatment" health state reflects the utility value of a stable disease NET with a level 3 or 4 diarrhea (typically defined as at least 7 BMs per day over baseline[11]). This is inconsistent with patients in the TELESTAR trial, who had 5 to 6 BMs per day at baseline, on average. Also, the use of utility values from the health-state valuation study led to a larger difference in utility values between the "remain on treatment" and "discontinue treatment" health states (i.e., 0.171) than that observed between response groups in the TELESTAR trial (0.073 based on the manufacturer's utility analysis[7]). Regarding data sources for the AE disutilities for the subsequent treatment-scenario analyses, the applicability of the utility decrements for elevated liver enzyme levels sourced from a tuberculosis study and the utility decrement for severe pain

Data Input	Description of Data Source	Comment
	population with NET,[6,18] tuberculosis,[19] or breast cancer.[20]	sourced from a breast cancer study is questionable. The utility decrements sourced from other studies in the NET population are appropriate.
Adverse events	Adverse events associated with subsequent therapies were modelled based on clinical studies from a targeted literature review if the reported AEs were severe or serious grade 3 to 4 AEs and had ≥ 5% annual incidence.	Acceptable.
Mortality	Overall survival was informed by the manufacturer's survival analysis of the survival data from the lanreotide arm of the CLARINET trial open-label extension. Scenario analyses attributed survival benefit to telotristat ethyl and applied HRs sourced from a midgut NET trial[21] and retrospective US surveillance data[22] to the CLARINET placebo-arm survival curve derived from the manufacturer's survival analysis.	Uncertain. Although source is appropriate in the short-term, extrapolating six-year survival data to fit 30-year time horizon introduces uncertainty. These sources were appropriately reserved for scenario analyses.
Costs and Resource Use		
Drugs and procedures	List price from Ontario formulary. Procedure costs were sourced from the Ontario Case Costing Initiative where possible. Clinician opinion was used to estimate the procedure cost of PRRT. As interferon–alfa 1a is not marketed in Canada, the cost of interferon–alfa 2a was used to estimate cost for this scenario. The cost of SIRT procedure was sourced from a conference proceeding.	Appropriate. Appropriate. Uncertain. Uncertain. Uncertain.
Administration	Ontario Schedule of Benefits and Fees for injections. Ontario public pharmacy dispensing fee.	Appropriate. Appropriate.
Adverse events	Costs of adverse events associated with subsequent therapies were sourced from OCCI.	Appropriate.
Resource use	Physician cost of monitoring patients was sourced from the Ontario Schedule of Benefits and Fees.	Appropriate. Uncertain.

Data Input	Description of Data Source	Comment
	Resource use varied with each type of therapy and was informed by clinician input.	

AE = adverse event; BM = bowel movement; CDR = CADTH Common Drug Review; CS = carcinoid syndrome; HR = hazard ratio; OCCI = Ontario Case Costing Initiative; NET = neuroendocrine tumour; PRRT= peptide receptor radionuclide therapy; SIRT = selective internal radiation therapy; SSA = somatostatin analogue.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Model Structure	
No adverse events were modelled in the manufacturer's base case. The TELESTAR trial reported one incidence of serious vomiting and nausea in the SSA monotherapy arm, but the manufacturer-consulted clinicians did not expect any serious adverse events with SSA monotherapy.	Appropriate. The CDR clinical report also did not find clear differences in notable adverse events.
Treatment	
The SSA dose for both SSA monotherapy and telotristat and SSA combination therapy are assumed to be the same.	Appropriate.
All patients were assumed to start responding at 6 weeks.	Acceptable as a simplifying assumption.
All patients continue to receive SSA monotherapy after telotristat ethyl discontinuation.	Uncertain. Although the safety profile of SSA may allow patients to continue receiving long-term SSA therapy, clinicians may switch patients to other therapies without SSA due to disease progression or lack of efficacy.
Patients do not discontinue SSA monotherapy.	
Initial response and discontinuation probabilities remain consistent for the entire 30-year time horizon.	Uncertain.
Telotristat ethyl does not have survival benefit in the manufacturer's base-case analysis.	Appropriate.
In scenario analyses with subsequent therapy, all patients are assumed to respond to subsequent therapy and do not discontinue the subsequent therapy.	Appropriate as a simplifying assumption for the scenario analysis.
Natural History	
Patients are assumed to have stable disease until death.	The impact of not capturing the natural history of the population is uncertain.
Weibull survival curve was assumed for the manufacturer's base-case analysis.	Acceptable. However, significant uncertainty is associated with the extrapolation of 6-year survival data to a 30-year period.
Adverse Events	
In scenario analyses with a subsequent therapy, the disutilities associated with each adverse event were applied in a way that assumed that each adverse event had an independent negative impact on quality of life.	Inappropriate. This is likely to overestimate the impact of adverse events on quality of life. For instance, a patient with all the listed adverse events would experience a disutility of −1.21.
Resource Use	
Patients are assumed to have the same 28-day follow-up frequency regardless of treatment response status.	Uncertain. The clinical expert consulted by CDR indicated that patients who respond to therapy may be followed less frequently (every three months) than those who do not (every one to two months).

CDR = CADTH Common Drug Review; SSA = somatostatin analogue.

Manufacturer's Results

The manufacturer's base-case results are presented in Table 13. The results of the manufacturer's scenario analyses are reported in Table 14.

Table 13: Summary of Results of the Manufacturer's Base Case

Comparator	Total Cost ($)	Incremental Cost ($)	Total QALYs	Incremental QALYs	ICUR ($ per QALY Gained)
SSA	290,440		5.104		
Telotristat ethyl in combination with SSA	424,209	133,769	5.262	0.158	846,693

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years; SSA = somatostatin analogue.

Table 14: Manufacturer's Scenario Analyses — Mean Probabilistic Results

Parameter	Scenario	Incremental Cost[a] ($)	Incremental QALYs[a]	ICUR[a] ($ per QALY Gained)
Time horizon	5 years	116,428	0.128	913,476
	10 years	132,287	0.155	851,129
	20 years	133,413	0.158	846,083
Cost and outcomes discount rate	0%	137,251	0.163	840,551
	3%	130,061	0.152	856,738
Time to response for telotristat and SSA combination therapy	0 weeks	134,007	0.165	811,397
Overall survival curve distribution	Exponential	139,963	0.170	825,069
	Log-logistic	135,925	0.162	841,506
	Log-normal	138,304	0.166	834,121
	Generalized gamma	134,171	0.159	843,431
Overall survival benefit hazard ratio source	Rinke et al. (2017)[21]	128,562	0.149	861,919
	Shen et al. (2014)[22] — distant stage disease	135,230	0.161	840,956
	Shen et al. (2014)[22] — local stage disease	127,825	0.148	863,196
SSA and telotristat probability of response	98%	280,001	0.435	644,191
Baseline SSA dose	Not assumed equal across treatment groups. Baseline SSA dose differed based on treatment group dosages reported in TELESTAR trial	132,006	0.158	835,373
Subsequent treatment market share	Average clinical opinion[b]	116,497	0.009	13,059,026
	100% Everolimus	66,951	0.012	5,688,121
	100% PRRT	123,974	0.011	10,969,690
	100% TACE	132,335	0.013	10,603,252
	100% TAE	132,152	0.013	10,314,529

ICUR = incremental cost-utility ratio; PRRT = peptide receptor radionuclide therapy; QALY = quality-adjusted life-years; RFA = radiofrequency ablation; SIRT = selective internal radiation therapy; SSA = somatostatin analogue; TACE = transcatheter arterial chemoembolization; TAE = transarterial embolization.

[a] The manufacturer did not report total costs and total QALYs for the scenario analyses. These results are based on modifications to the manufacturer's base case.

[b] The average market share of each subsequent therapy (de-bulking surgery, everolimus, interferon-alfa, PRRT, RFA, SIRT, TACE, and TAE) were informed by clinicians.

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