Common Drug Review

Pharmacoeconomic Review Report

September 2015

Drug	linaclotide (Constella)
Indication	For the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.
Listing request	For treatment of IBS-C in adults.
Manufacturer	Actavis Specialty Pharmaceuticals Co

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

APC	abdominal pain and complete spontaneous bowel movement
CDR	CADTH Common Drug Review
GP	general practitioner
IBS-C	irritable bowel syndrome with constipation
ITT	intention-to-treat
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Linaclotide (Constella)
Study Question	Determine the cost-effectiveness of linaclotide compared with placebo for the treatment of IBS-C in adult patients
Type of Economic Evaluation	CUA
Target Population	Patients with IBS-C as per the population included in the clinical trials
Treatment	Linaclotide
Outcome(s)	QALYs
Comparator	No treatment – placebo as per the control group of the clinical trials
Perspective	Ministry of Health (societal also included in additional analysis)
Time Horizon	52 weeks
Results for Base Case	The manufacturer reported the incremental cost per QALY for linaclotide compared with no treatment to be $17,758 — based on an incremental cost of $604 and incremental QALY gain of 0.0344
Key Limitations	CDR noted several limitations: • Assumptions around reduced resource consumption with linaclotide are not supported by the clinical evidence, and results from clinical trials suggest limited clinical benefit in terms of response definitions (e.g., APC and CSBM) • Assumptions around drug costs associated with non-responders with linaclotide were not justified • Utility values for health states were assumed to differ between treatments • No other interventions were considered other than no treatment.
CDR Estimate	CDR considered in reanalyses: • No difference in resource use between responders and non-responders • Assumption that non-responders stop linaclotide at 12 weeks where no response is observed • Assumed no treatment-related differences in utilities within health states • Based on the revised assumptions, CDR reported the incremental cost per QALY for linaclotide compared with no treatment to be $102,376; based on an incremental cost of $844 and incremental QALYs of 0.0082 • A significant reduction in QALYs gained is observed under the CDR scenario • A price reduction of 50% would be required for the ICUR to fall to ~$49,000 per QALY for linaclotide compared with no treatment.

APC = abdominal pain and complete spontaneous bowel movement; CDR = CADTH Common Drug Review; CSBM = complete spontaneous bowel movement; CUA = cost-utility analysis; IBS-C = irritable bowel syndrome with constipation; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY

Background

Linaclotide (Constella) is a 14-amino-acid peptide that is approved for treatment for irritable bowel syndrome with constipation (IBS-C). The manufacturer requested listing for adults with IBS-C, aligned with the approved indication. The recommended dose is 290 mcg once daily, at a cost of $5.30 per 290 mcg tablet.[1]

The manufacturer submitted a cost-utility analysis (CUA) based on a decision tree evaluating the cost-effectiveness of linaclotide in adult patients with IBS-C when compared with no treatment (placebo).[2] The decision tree characterized patients as falling into one of three final states: failure (discontinuation); failure (no response); and improvement (response). Response was defined as having the desired improvement measured by the abdominal pain and complete spontaneous bowel movement in six out of 12 weeks (APC 3+1 6/12). Responders were assumed to continue treatment for the duration of the time horizon (52 weeks). Patients who moved into the failure category were assumed to receive treatment for 30 days. Utility values were assigned for the failure and improvement states, and were assumed to vary by treatment at baseline — differences were assumed to continue after treatment was curtailed. Costs were assigned to the failure and improvement states with minimal resource use assigned to the improvement state. The analysis was undertaken from a ministry of health perspective and conducted over a one-year time horizon.

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified a number of limitations with the manufacturer's economic evaluation around data inputs used in the model.

The manufacturer assumed that patients on linaclotide who failed to achieve a response would stop therapy after 30 days; however, the outcome measure used to define response relates to 12 weeks of outcomes. Thus, an assumption of 12 weeks of treatment for patients who are non-responders may be more appropriate.

The model is defined by two states: improvement and failure. The manufacturer assumed differential utility values within these states for placebo and linaclotide, which is inappropriate practice. If health status is assumed to vary within health states, then more refined definitions of states should be used. Further, as patients who fail on therapy are assumed to discontinue after 30 days, the utility values associated with linaclotide should not apply.

The clinical trials found no difference in resource use between linaclotide and placebo patients. The manufacturer, however, assumed negligible resource use for patients who were responders, which benefits linaclotide. Thus, there is little justification for the assumption made within the analysis.
The manufacturer reported that the incremental cost per quality-adjusted life-year (QALY) for linaclotide compared with no treatment was $17,758 (an incremental cost of $604 and incremental QALYs of 0.0344). Revised analysis accounting for the above limitations leads to incremental cost per QALY gained of $102,376 for linaclotide compared with no treatment.

Note, the manufacturer compared linaclotide with placebo in its analysis, where no other comparators were considered. Although linaclotide is the only treatment specifically indicated for IBS-C, other therapies indicated for a broader diagnosis could have been considered (e.g., fibre, laxatives). Thus, the cost-effectiveness of linaclotide compared with other treatment options that could provide symptom relief cannot be addressed.

Conclusions

Based on the manufacturer's submitted price, the daily cost of linaclotide is $5.30 or $1,935 annually. When accounting for limitations identified with the manufacturer's economic submission, CDR noted a likely incremental cost per QALY (incremental cost-utility ratio [ICUR]) of $102,376 for linaclotide when compared with no treatment. In this scenario, a 50% price reduction would be required for the ICUR to fall to $49,000.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) using a decision tree model that compared linaclotide with placebo (no treatment) in patients with irritable bowel syndrome with constipation (IBS-C).[2] The analysis was undertaken from both a ministry of health and societal perspective, over a one-year time horizon. Focus in this review is on results from the ministry of health perspective.

The probability of response and the probability of discontinuation were obtained for both linaclotide and placebo from LIN-MD-31 and MCP-103-302.[3,4] Response was defined as having the desired improvement measured by the abdominal pain and complete spontaneous bowel movement in six out of 12 weeks (APC 3+1 6/12). For each week in the treatment period, a weekly APC 3+1 responder was a patient who had at least three complete spontaneous bowel movements (CSBMs) for the week and an increase of at least one CSBM from baseline for that week, and also had a decrease of at least 30% in the mean abdominal pain score for that week compared with baseline. Responders were assumed to continue treatment for the duration of the time horizon (52 weeks).

The probability of response for both placebo and linaclotide were assumed to be based on the intention-to-treat (ITT) data from the LIN-MD-31 and MCP-103-302 clinical trials (139/797 (17.4%) and 271/805 (33.7%), respectively). However, the actual denominators for the ITT populations from the clinical review were 798 and 806, respectively.

The probability of discontinuation for both placebo and linaclotide were based on the observed premature discontinuation rates from the LIN-MD-31 and MCP-103-302 clinical trials (162/799 (20.3%) and 202/807 (25.0%), respectively). The denominator for placebo corresponds with the safety population with the clinical trials, but the denominator for linaclotide does not match either the ITT, safety, or complete data set population. The actual number of discontinuations in the placebo groups was 160, not 162. Given the ITT nature of the data on response, it is possible that a proportion of discontinuers were also patients who were judged as responders. Allowance for this within the analysis would make linaclotide less cost-effective. The probability of continuation with no response was simply 1 minus the sum of the other probabilities. The report states that the patients who discontinued therapy would stop therapy 30 days after discontinuation and those experiencing a lack of response would stop therapy after 30 days of no response. However, within the model, those who discontinue therapy were allocated 30 days of treatment and those who did not respond were allocated 30 days of treatment, despite the outcome of response being based on 84 days of observation.

Utility values were obtained from LIN-MD-31 and MCP-103-302 clinical trials, where the EuroQol 5-Dimensions Questionnaire (EQ-5D) was administered at baseline and at week 12. Utility values were assigned for the failure and improvement states, and were assumed to vary by treatment at baseline, with higher utility values for linaclotide patients than placebo patients. Differences were assumed to continue after treatment was curtailed.

TABLE 2: TREATMENT-DEPENDENT UTILITIES

	Linaclotide	No Treatment/Placebo
Response	[redacted]	[redacted]
Non-response	[redacted]	[redacted]

Source: Manufacturer's pharmacoeconomic submission.[2]

Costs were assigned to the failure and improvement states, with minimal resource use assigned to the improvement state (only 30% of responders were assumed to have only one general practitioner [GP] visit per annum). Health care resources considered were physician (GP and specialist) visits, emergency room (ER) visits, hospitalizations, and drug therapies. Unit costs were based on the Ontario physician schedule and the Canadian Institute for Health Information (CIHI) Patient Cost Estimator tool. Resource use for patients who were responders was assumed to be minimal (one GP visit per annum) based on expert opinion. The health care costs (excluding linaclotide) for a responder was $23 per annum compared with $952 for non-responders. For patients who were non-responders, a variety of therapies for symptom management were considered as possible resource use, although no benefit was assigned to any of these therapies. The costs of these alternative prescription therapies were $220 for non-responders and zero for responders. The annual cost of treatment with linaclotide for responders was $1,934.50.

2. MANUFACTURER'S BASE CASE

The manufacturer reported in its base case that linaclotide was associated with an incremental cost of $1,394 from a ministry of health perspective and a gain of 0.8469 quality-adjusted life-years (QALYs). When compared with placebo, linaclotide was $604 more costly and associated with a gain of 0.0344 QALYs, for an incremental cost-utility ratio (ICUR) of $17,578.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Among the manufacturer's sensitivity analyses, narrowing the time horizon to 12 weeks increased the incremental cost-effectiveness ratio (ICER) to $28,133 while use of treatment-independent utility values increased the ICER to $73,318. A probabilistic sensitivity analysis suggested that the probability linaclotide was cost-effective at a threshold of $50,000 per QALY was 82.0% (Figure 3).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Choice of comparators.** The manufacturer considered the comparison of linaclotide with no treatment/placebo in its analysis. No other comparators were considered. Although linaclotide is the only treatment specifically indicated for IBS-C, other therapies indicated for a broader diagnosis could have been considered (e.g., Table 4). The analysis does assume that patients who are treatment failures do receive symptom management therapies, but assigns only costs and no benefits to these therapies. Thus, the cost-effectiveness of linaclotide compared with other treatment options that could provide symptom relief cannot be addressed. Furthermore, given that non-responders were allotted the costs of treatments for symptom management, it would appear logical that some assumption around the benefit accrued from these therapies should be included.

- **Treatment discontinuation.** For patients who experienced non-response on linaclotide, it was assumed that they would stop therapy after 30 days. However, the outcome measure used to define response relates to 12-week outcomes. Thus, an assumption of 12 weeks of treatment of patients who failed to respond to therapy may be more appropriate.
- **Utility values.** The manufacturer assumed differential utility values within "improvement" and "failure" states for placebo and linaclotide. This is inappropriate practice, as if health status is assumed to vary within health states, more refined definitions of states should be used. Further, as patients who fail on therapy are assumed to discontinue after 30 days, the utility values associated with linaclotide should not apply. The assumption made in one of the manufacturer's sensitivity analyses, which assumed treatment-independent utility values, should be employed as base case.
- **Resource use.** The manufacturer assumed negligible resource use for patients who were responders, which benefits linaclotide. No difference in resource use between linaclotide and placebo groups was observed in the clinical trials. Thus, there is little justification for the assumptions made within the analysis. Analysis assuming equal resource use would appear more justifiable.

5. CADTH COMMON DRUG REVIEW ANALYSES

Results of reanalyses are presented in Table 11 and summarized here. The CADTH Common Drug Review (CDR) base-case reanalysis comprised adjustments based on three specific issues: treatment discontinuation, utility values, and resource use.

Further analysis incorporated the issue of symptom therapy through other alternate prescription therapies. This was addressed in turn through three alternate approaches: reducing the time horizon of the model to 12 weeks, assuming a 10% response rate from alternate therapies, and assuming the same costs of alternate therapies for responders and non-responders.

1. **Treatment discontinuation:**
   For patients who experienced non-response on linaclotide it was assumed that they would stop therapy after 84 days, given that response was based on a definition relating to 12 weeks of outcomes. This increased the ICUR from $17,578 to $21,017 for linaclotide compared with no treatment.
2. **Utility values:**
   Reanalysis was based on treatment-independent utility values. As per the sensitivity analysis detailed above, this increased the ICUR to $73,318.
3. **Resource use:**
   Reanalysis was conducted assuming equal resource use for responders and non-responders. Given the clinical trial findings of no difference in resource use between linaclotide and placebo, this assumption appears more justifiable. Analysis still assumed use of symptom management therapy only in non-responders. This increased the ICUR to $20,938.

6. CADTH COMMON DRUG REVIEW BASE CASE — COMBINATION OF FIRST THREE LIMITATIONS

Reanalysis based on the revised assumptions relating to treatment discontinuation, utility values, and resource use found the incremental cost per QALY gained for linaclotide to be $102,376. This is considered the CDR base case. A probabilistic sensitivity analysis was conducted for this scenario and found the probability that linaclotide was cost-effective based on a $50,000 threshold was 2.3% (Table 11).

Additional CADTH Common Drug Review Analyses

The following additional CDR analyses were conducted using the CDR base case:

- **Inclusion of 12-week time horizon:**
  Reanalysis based on the CDR base case with a 12-week time horizon found the incremental cost per QALY gained for linaclotide to be $196,464 when compared with no treatment.
- **Equal costs of alternative prescription therapies:**
  Reanalysis based on the assumption of the same costs of alternative prescription therapies for responders and non-responders resulted in an incremental cost per QALY gained for linaclotide compared with no treatment at $111,058.
- **Benefits from alternative prescription therapies for non-responders:**
  A further reanalysis based on the CDR base case speculatively assumed a 10% response rate with non-responders taking alternative prescription therapies. This found the incremental cost per QALY gained for linaclotide to be $106,020.

Price Reduction Scenarios

Price reduction analyses were conducted based on the revised CDR base case. A 50% price reduction would lead to an incremental cost per QALY gained of $49,366 (Table 12).

7. PATIENT INPUT

Through the CADTH Patient Input process, patient groups identified the following concerns with IBS-C:

- Patients experience symptoms such as increased pressure on the bowels, bloating, abdominal cramping, back pain, general malaise, poor appetite, feelings of rectal pressure or fullness, and a sensation of incomplete evacuation. In addition, hemorrhoids, anal fissures, diverticular disease, rectal bleeding, and rectal prolapse are often experienced as complications from intense straining while trying to pass stool. These symptoms were captured in outcome measures included in the clinical trials and further used in the manufacturer's economic evaluation.
- Impacts on activities of daily living (ADL) for the patient as well as caregivers were cited as concerns. The manufacturer attempted to account for this by considering a societal perspective; however, information on impact on patient ADL and caregiver impact was not captured in the clinical studies. Furthermore, the assumptions relating to the societal costs with and without treatment response were not based on data.

8. CONCLUSIONS

The manufacturer reported that the incremental cost per QALY for linaclotide is $17,578 compared with placebo. However, based on several limitations with the submitted analysis, the CDR reanalysis suggests an ICER of at least $102,376.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 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.

TABLE 3: COST COMPARISON TABLE FOR IRRITABLE BOWEL SYNDROME

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Cost ($)	Annual Cost ($)
Linaclotide (Constella)	**290 mcg**	**Tab**	**$5.30000**	**290 mcg daily**	**$5.30**	**$1,934.50**

Tab = tablet.
Source: Manufacturer's submitted price.

The following supplemental table provides information on drugs used in the management of symptoms associated with IBS-C.

TABLE 4: COST COMPARISON TABLE FOR DRUGS USED FOR SYMPTOMATIC TREATMENT FOR IRRITABLE BOWEL SYNDROME

Drug Generic Name	Strength	Dosage Form	Price ($)	Recommended Daily Dose	Daily Cost ($)
Bisacodyl (Dulcolax and generics)	5 mg	tablet	0.0450	5 mg to 15 mg	0.05 to 0.14
	5 mg 10 mg	suppository suppository	1.0933 0.5500	10 mg	0.55
Docusate calcium (generics)	240 mg	capsule	0.1287	240 mg	0.13
Docusate sodium (Colace and generics)	100 mg	capsule	0.0328	100 mg to 200 mg	0.03 to 0.07
	4 mg/mL 10 mg/mL	oral liquid oral liquid	0.0232 0.1770	100 mg to 200 mg	1.77 to 3.54
Lactulose (generics)	667 mg/mL	oral liquid	0.0145	15 mL to 30 mL once to twice daily	0.22 to 0.88
Mineral Oil (Fleet enema)	130 mL solution	enema	3.2600	One enema as needed	3.26
Sennosides A & B / Senna (Senokot)	1.7 mg/mL	syrup	0.0318	10 mL to 15 mL once or twice daily	0.32 to 0.94
	8.6 mg	tablet	0.0595	2 to 4 tablets once or twice daily	0.12 to 0.48
Sodium biphosphate & sodium phosphate (Fleet and generics)	160/60 mg/mL	120 mL rectal solution	0.0205	One enema as needed	2.46
Sodium citrate & Sodium Lauryl Sulfoacetate (Microlax)	5 mL	enema liquid	0.9152	5 mL or 10 mL	0.92 to 1.83

Source: Ontario Drug Benefit (April 2014).

APPENDIX 2: SUMMARY OF KEY OUTCOMES

The following are based on the manufacturer's results.

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS LINACLOTIDE RELATIVE TO NO TREATMENT?

Linaclotide Versus No Treatment	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	$17,758 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: 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 7: AUTHOR INFORMATION

Authors	Affiliations
[redacted]	Pivina Consulting

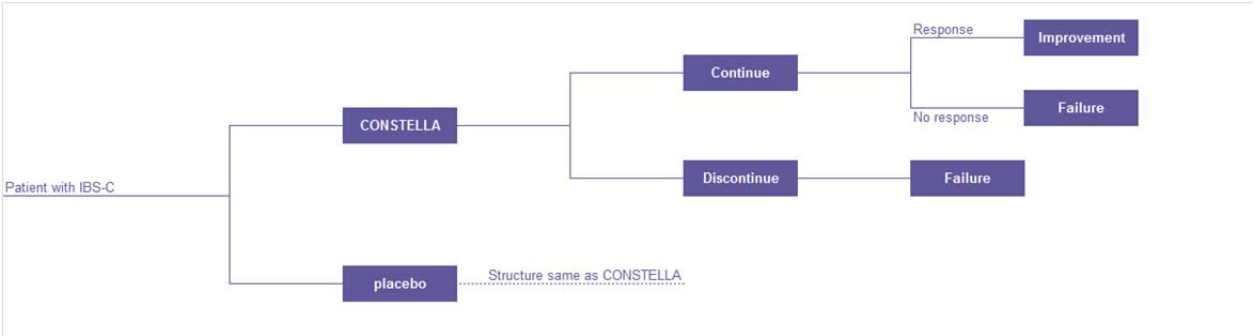
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The decision tree is simple in that there are only two probabilities within the model and three potential final states: failure (discontinuation); failure (no response); and improvement (response). The tree is presented as follows by the manufacturer:

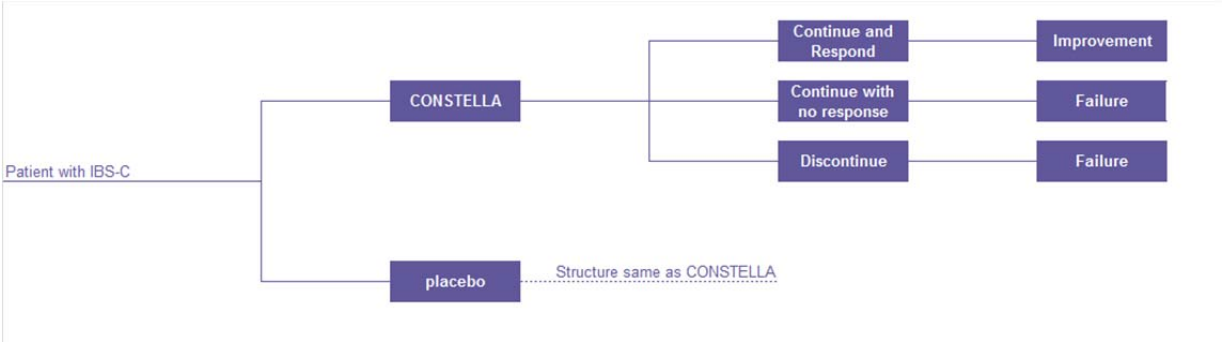
FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



IBS-C = irritable bowel syndrome with constipation.
Source: Manufacturer's Pharmacoeconomic Submission.[2]

However, this is not an accurate reflection of the model, given the basis of calculations involved. The true structure of the model is as follows:

FIGURE 2: ACTUAL MODEL STRUCTURE



IBS-C = irritable bowel syndrome with constipation.

TABLE 8: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Pooled analysis of LIN-MD-31 and MCP-103-302	
Utilities	Pooled analysis of LIN-MD-31 and MCP-103-302	
Resource use	Expert opinion	Biases in favour of linaclotide — tested in CDR analyses
Adverse events	Not included	
Mortality	Not included	
Costs		
Drug	Linaclotide — Manufacturer Other treatments — ODB and RAMQ (year not cited)	
Event	Ontario Ministry of Health, CIHI (year not cited)	

CDR = CADTH Common Drug Review; CIHI = Canadian Institute for Health Information; ODB = Ontario Drug Benefit; RAMQ = Régie de l'assurance maladie Québec.

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Utilities for health states are treatment-dependent.	In economic evaluation, health states should be specified such that the utility values associated with them should be treatment-independent. If it is felt that there are differences within the same health state between treatments, this should be appropriately handled by providing a more complete range of health states. The assumption of treatment-dependent utility values was tested in CDR analyses.
Health care resource use varies by response.	This was not observed in clinical trials.
No treatment is an appropriate comparator.	While no other treatments are specifically indicated for IBS-C, in actual practice a number of pharmacologic drugs (and exercise) are used for the management of symptoms. As this represents current care, this should have been considered.
APC responder 6/12 weeks is an appropriate outcome.	Response is subjective in nature, and as such it is difficult to define one response measure that may apply to all patients. While this is reasonable, it is unclear whether this definition will be used consistently in clinical practice.

APC = abdominal pain and complete spontaneous bowel movement; CDR = CADTH Common Drug Review; IBS-C = irritable bowel syndrome with constipation.

Manufacturer's Results

The manufacturer reported in its base case that linaclotide was associated with an incremental cost of $1,394 from a ministry of health perspective and a gain of 0.8469 quality-adjusted life-years (QALYs). When compared with placebo, linaclotide was $604 more costly and associated with a gain of 0.0344 QALYs, for an incremental cost-utility ratio (ICUR) of $17,578.

TABLE 10: MANUFACTURER'S BASE-CASE ANALYSIS

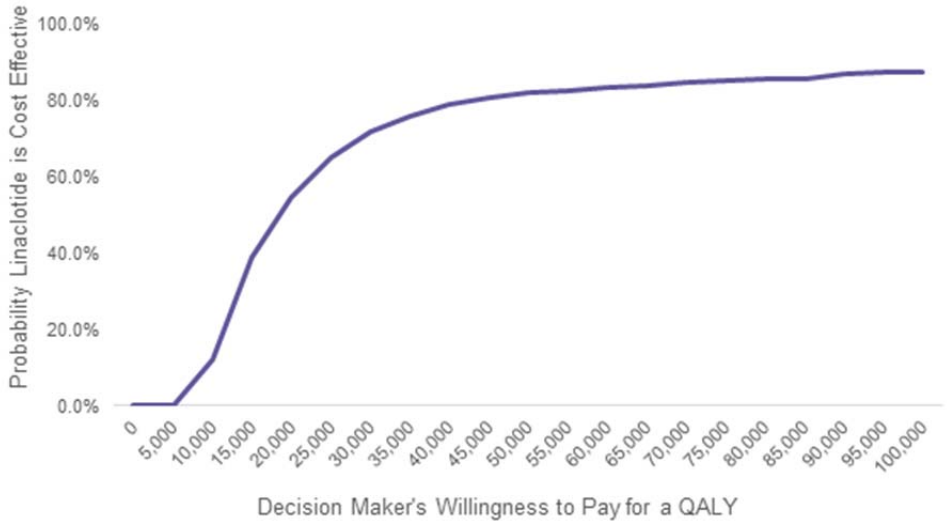
	Linaclotide	Placebo	Incremental
Cost per Patient	$1,394	$790	$604
QALYs per Patient	0.8469	0.8125	0.0344
		ICUR	**$17,578**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

When considering a societal perspective, the manufacturer included the cost of lost work productivity. Lost productivity was based on the need to attend physician and/or emergency room (ER) visits and hospitalizations, in addition to "sick days". Assumptions around lost time for physician visits appeared to be based on assumed time and the time lost to "sick days" was captured as part of the clinical trials. The manufacturer calculated a total cost of $4,492 per patient over 52 weeks for non-responders compared with $91 for responders, based only on time to attend physician visits. The manufacturer reports that linaclotide dominates no treatment — 0.034 QALYs gained and a cost savings of $113. This result is based on speculative differences in societal costs between treatment responders and non-responders, which was not based on the trial evidence.

Among the manufacturer's sensitivity analyses, narrowing the time horizon to 12 weeks increased the incremental cost-effectiveness ratio (ICER) to $28,133 while use of treatment-independent utility values increased the ICER to $73,318. A probabilistic sensitivity analysis suggested that the probability linaclotide was cost-effective at a threshold of $50,000 per QALY was 82.0% (Figure 3).

FIGURE 3: MANUFACTURER'S COST-EFFECTIVENESS ACCEPTABILITY CURVE



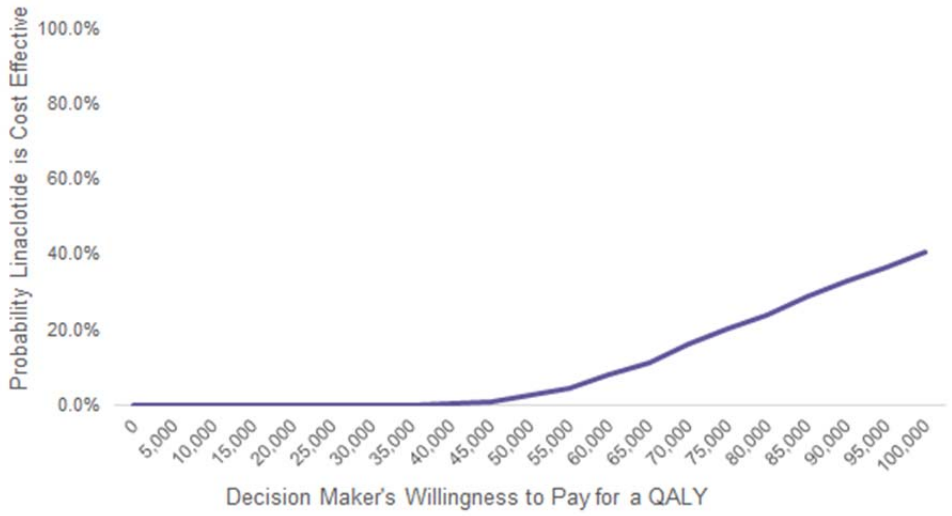
QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[2]

CADTH Common Drug Review Reanalysis

Reanalysis based on the revised assumptions relating to treatment discontinuation, utility values, and resource use found the incremental cost per QALY gained for linaclotide to be $102,376.

A probabilistic sensitivity analysis was conducted for this scenario and found the probability that linaclotide was cost-effective based on a $50,000 threshold was 2.3%.

FIGURE 4: CADTH COMMON DRUG REVIEW COST-EFFECTIVENESS ACCEPTABILITY CURVE



QALY = quality-adjusted life-year.

The full set of CADTH Common Drug Review (CDR) analyses is presented in Table 11.

TABLE 11: CADTH COMMON DRUG REVIEW REANALYSES

Scenario		Incremental Cost of Linaclotide	Incremental QALYs With Linaclotide	Incremental Cost per QALY Gained (vs. No Treatment)
	Manufacturer's submission	$604	0.0344	$17,758
1	**Treatment discontinuation after 12 weeks with non-response**	$722	0.0344	$21,017
2	**Treatment-independent utility values**	$604	0.0082	$73,318
3	**No differences in resource use between responders and non-responders**	$720	0.0344	$20,938
4 (1-3)	**Combination of above three (CDR base case)**	$844	0.0082	$102,376
5 (based on 4)	**CDR base case plus 12-week time horizon**	$374	0.0019	$196,464
6 (based on 4)	**CDR base case plus equal costs of alternative prescription therapies**	$874	0.0082	$106,020
7 (based on 4)	**CDR base case plus 10% response rate with alternative prescription therapies**	$844	0.0074	$113,751

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year; vs. = versus.

Price reduction analyses were conducted based on the revised CDR base case to assess the incremental cost per QALY gained associated with linaclotide based on a range of price reductions (from 10% to 90%). A 50% price reduction would lead to an incremental cost per QALY gained of $49,366 (Table 12).

TABLE 12: IMPACT OF PRICE REDUCTIONS ON CADTH COMMON DRUG REVIEW BASE CASE

Scenario	Incremental Cost per QALY Gained
CDR base case	$102,376
10% price reduction	$91,774
20% price reduction	$81,172
30% price reduction	$70,570
40% price reduction	$59,968
50% price reduction	$49,366
60% price reduction	$38,764
70% price reduction	$28,162
80% price reduction	$17,560
90% price reduction	$6,958

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year.

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