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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

ELUXADOLINE (VIBERZI)

(Allergan Pharma Co.)

Indication: For the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

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Abbreviations

CDR	CADTH Common Drug Review
EQ-5D	EuroQol 5-Dimensions questionnaire
IBS-D	irritable bowel syndrome with diarrhea
IBS-QoL	Irritable Bowel Syndrome Quality of Life questionnaire
ICUR	incremental cost-utility ratio
NICE	National Institute for Health and Care Excellence
NPT	no pharmacological therapy
PI	pain improved
PNI	pain not improved
QALY	quality-adjusted life-year
SMC	Scottish Medicines Consortium

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Eluxadoline (Viberzi) 75 mg and 100 mg oral tablets
Study Question	The objective of this analysis was to translate the clinical outcomes of IBS-3001 and IBS-3002 into a robust and clinically meaningful health economic evaluation to determine the cost-utility of eluxadoline compared with no pharmacological therapy (NPT) as the current best supportive care for the treatment of patients with diarrhea-predominant irritable bowel syndrome (IBS-D).
Type of Economic Evaluation	Cost-utility analysis (CUA)
Target Population	Adult patients with IBS-D who have not responded adequately to or cannot tolerate current treatment options, such as loperamide. • Base-case analysis: reflective of intent-to-treat population from IBS-3001/3002 • Scenario analysis: subgroup analysis in patients previously treated with loperamide
Treatment	Eluxadoline 100 mg taken orally twice daily.
Outcome	Quality-adjusted life-year (QALY)
Comparator	No pharmacological therapy — placebo
Perspective	Public-payer perspective
Time Horizon	5 years
Results for Base Case	The probabilistic incremental cost-utility ratio (ICUR) for eluxadoline vs. NPT: • $17,384 per QALY • Prior-loperamide-use population: $19,742 per QALY
Key Limitations	• The observed persistence with treatment in the clinical trials shows little difference between eluxadoline and NPT, but once extrapolated based on the economic model, a long-term persistence benefit for eluxadoline over NPT was found. The health state utilities in the trials were generally higher in the eluxadoline arm, and because fewer people on eluxadoline stopped treatment once the data were extrapolated, the magnitude of QALY gains in the eluxadoline arm was increased and may be overestimated. • Treatment persistence was modelled using separate parametric curves for placebo (used to represent NPT) and eluxadoline, despite the lack of a comparative analysis that justifies a persistence benefit for eluxadoline over placebo. • All 3 trials were placebo-controlled and had a high placebo response rate. Based on the manufacturer's modelled stopping rule, at 4 weeks with return to baseline utility, a larger proportion of patients stopped treatment at four weeks and returned to baseline utility in the NPT arm (50.1%) compared with the eluxadoline arm (38.7%). This drives a substantial increase in the estimated QALY gain for eluxadoline and effectively strips out the observed placebo response from 50.1% of the control arm, such that the modelled benefits for those continuing on eluxadoline are no longer fully controlled for placebo response. • Use of Rome III criteria to diagnose IBS-D is not common in clinical practice. Therefore, patients presenting in clinical practice could have less-severe symptoms than patients enrolled in the clinical trials. This could lead to the actual benefits of eluxadoline being lower than observed in the trials, when used in a less-severe population. • The outcome measures used in the economic analysis (IBS-QoL and pain) to model the clinical effects of eluxadoline are not commonly used in clinical practice, which relies predominantly on subjective assessments by patients. • The manufacturer's assumption of a continued benefit of 25% for eluxadoline after stopping treatment, which is maintained over the lifetime of the model, was not supported by any long-term clinical data. • Ongoing annual scoping procedures included by the manufacturer are not common in clinical practice.

Key Limitations	• The manufacturer included the clinical effectiveness inputs from study IBS-2001, a phase II dose-finding, proof-of-concept study that was not included in the CDR Clinical Review for eluxadoline because it extends beyond the objective of the analysis as stated.
CDR Estimates	• There is uncertainty associated with the estimated cost-effectiveness of eluxadoline compared with NPT in the indicated populations for which the manufacturer is seeking reimbursement given the uncertainty with the estimation of clinical effects of eluxadoline after the discontinuation of treatment. • CDR conducted a probabilistic base-case analysis assuming patients on eluxadoline and patients on NPT would have the same utility values by using a single extrapolation curve for both arms (similar persistence values), assuming no relative benefit after stopping treatment and no ongoing costs for scoping beyond the first year. • In the CDR base case, the ICUR was $105,829 per QALY for eluxadoline compared with NPT. • A scenario analysis was undertaken by CDR applying similar values for persistence data and early stopping rates for both eluxadoline and NPT, assuming no relative benefit of eluxadoline after stopping treatment and no ongoing scoping costs beyond the first year, resulting in an ICUR of $121,004 per QALY for eluxadoline compared with NPT. • Price-reduction analyses using the CDR base cases indicate a price-reduction range of 50% to 60% may be required for eluxadoline to result in an ICUR of $50,000 per QALY.

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; IBS-D = irritable bowel syndrome with diarrhea; ICUR = incremental cost-utility ratio; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Drug	Eluxadoline (Viberzi)
Indication	For the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults
Reimbursement Request	As per indication
Dosage Form(s)	75 mg and 100 mg oral tablets
NOC Date	January 26, 2017
Manufacturer	Allergan Pharma Co.

Executive Summary

Background

Eluxadoline (Viberzi) is a mixed mu opioid receptor agonist and delta opioid receptor antagonist, and is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D).[1] The recommended dosage of eluxadoline is 100 mg taken orally twice daily with food.[1] For patients who are unable to tolerate the 100 mg dose, 75 mg taken orally twice daily with food is recommended.[1] The manufacturer submitted a price of $2.26 per tablet for both the 75 mg and 100 mg strengths ($4.51 per day).[2] The average annual cost for eluxadoline is $1,620 per patient.

The manufacturer submitted a cost-utility analysis for eluxadoline compared with no pharmacological therapy (NPT) for the treatment of patients with IBS-D.[2] The analysis was based on a Markov model in which patients were followed over a five-year time horizon using four-week cycles based on the time points of data collection in the IBS-2001 (Dove et al.),[3] IBS-3001, and IBS-3002 studies (Lembo et al.).[4] The Markov model consisted of 17 health states: 16 states based on levels of improvements in Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QoL) and pain scores and whether patients remain on treatment (continue) or discontinue; and a death state.[2] Clinical effectiveness was informed by the IBS-2001, IBS-3001, and IBS-3002 studies using a composite outcome of pain and stool consistency.[2,3,5] Patient demographics at baseline were based on pooled data from the intention-to-treat population of the IBS-2001, IBS-3001, and IBS-3002 studies (average age of patients was 44 to 47 years, while IBS onset was between the ages of 20 and 30 years).[2] For patients who stopped treatment after four weeks, the manufacturer carried forward the patient's last observed quality of life for the rest of the model, and used persistence data to capture patients who discontinue eluxadoline or NPT after four weeks until the end of the model time horizon. Persistence on treatment with eluxadoline and placebo were collected until week 12 in IBS-2001, until week 26 in IBS-3002, and until week 52 in IBS-3001.[2] A Kaplan–Meier estimator provided pooled persistence from all three studies. To model persistence over the model time horizon, the manufacturer fitted parametric distributions to the Kaplan–Meier data. Upon stopping treatment, patients incurred no treatment cost and incurred disease-related costs based on the proportion adequately or inadequately relieved at their last observation prior to discontinuation. Patients who discontinued eluxadoline were assumed to maintain 25% of the relative benefit for the remainder of the model, despite having stopped treatment. Utility values

were based on EuroQol 5-Dimensions questionnaire data from the IBS-2001 study.[2,3] Both outcomes and costs accrued beyond the first year of the model were discounted at a rate of 1.5%, as per CADTH guidelines.[6] The analyses took the perspective of the publicly funded health care system in Canada.[2]

The manufacturer reported that eluxadoline (100 mg) resulted in total costs of $5,320 per patient compared with $3,442 for NPT, and total quality-adjusted life-years (QALYs) of 3.475 compared with 3.367 in NPT. This resulted in a probabilistic incremental cost-utility ratio (ICUR) of $17,384 per QALY for eluxadoline 100 mg compared with NPT. An alternative analysis was conducted based on a pre-specified prospective subgroup analysis of IBS-3001/3002 in patients previously treated with loperamide; the resulting ICUR for eluxadoline increased to $19,742 per QALY compared with NPT.

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified several limitations with the manufacturer's submitted analysis. First, persistence with treatment in the trial did not appear to be different between the eluxadoline arm and the NPT arms but, once extrapolated in the economic model using separate parametric curves for NPT and eluxadoline (despite the lack of a comparative analysis that justified a persistence benefit for eluxadoline over NPT), fewer people receiving eluxadoline stopped treatment compared with NPT. As a result, and given that patients on eluxadoline were generally in better health states, the magnitude of QALY gains for those on eluxadoline increased.

Second, all three placebo-controlled trials had a high placebo response rate (that is, placebo improved outcomes). Based on the manufacturer's modelled stopping rule — at four weeks with return to baseline utility — a larger proportion of patients stopped treatment at four weeks and returned to baseline utility in the NPT arm (50.1%) compared with the eluxadoline arm (38.7%). This drives a substantial increase in the estimated QALY gain for eluxadoline and effectively strips out the observed placebo response from 50.1% of the control arm, such that the modelled benefits for those continuing on eluxadoline are no longer fully controlled for placebo response.

In addition, the clinical trials for eluxadoline used the Rome III criteria to diagnose patients with IBS-D. Based on feedback from the clinical expert consulted for this review, the use of the Rome III criteria in clinical practice is not common. Therefore, patients presenting in actual clinical practice could have less-severe symptoms than patients enrolled in the trials. The difference in severity between trial populations and as seen in clinical practice could lead to the actual (absolute) benefits of eluxadoline being lower than observed in the trials.

The efficacy outcomes for eluxadoline used in the economic model (IBS-QoL and pain) were not the primary outcomes of the clinical trials (a composite response of pain and stool consistency) and are also not commonly used in clinical practice as confirmed by the clinical expert. The discrepancy in outcomes undermines the certainty over the true efficacy of eluxadoline when used in clinical practice.

Further, the manufacturer applied a continuing benefit of eluxadoline (25% relative benefit) after stopping treatment and maintained it over the time horizon of the model (i.e., five years). No longitudinal data were presented to verify this benefit.

Finally, the manufacturer applied annual ongoing costs of scoping (over the five-year time horizon). Based on clinical expert opinion, scoping is only done in high-risk patients with intervals of two to three years (not ongoing).

The manufacturer included the clinical effectiveness inputs from study IBS-2001, a phase II dose-finding, proof-of-concept study. The CDR clinical reviewer did not include IBS-2001, noting several limitations with the inclusion and exclusion criteria, the primary and secondary end points being subjective, and the use of a composite end point that utilizes a non-validated outcome (the worst abdominal pain score). The inclusion of the information conflicts with the objective of the manufacturer's economic evaluation, considering the results of IBS-3001 and IBS-3002. Further details are available in the CDR Clinical Review for eluxadoline in Appendix 5.

In addition, the manufacturer conducted an alternative analysis in patient population with prior loperamide use based on a post hoc subgroup analysis that stratified patients who reported loperamide use in the year prior to study enrolment. The subgroup analysis was not pre-specified, no baseline characteristics were reported to allow assessment of potential imbalances in group population, and, with further stratification, it is no longer considered representative of a randomized population. As such, this subgroup analysis was only considered in exploratory analyses.

CDR conducted a probabilistic scenario analysis that assumed patients on eluxadoline and those on NPT would have similar persistence data, assumed no relative benefit after stopping treatment, and assumed no ongoing costs for scoping beyond the first year. The result of the CDR scenario analysis was an ICUR of $105,829 per QALY for eluxadoline compared with NPT. In an additional scenario analysis, CDR applied a similar stopping rule at four weeks for both eluxadoline and NPT to control for the placebo response, which resulted in an ICUR of $121,004 per QALY for eluxadoline compared with NPT.

Conclusions

The key limitations of the submitted economic analysis as identified by CDR were the use of separate parametric curves to model treatment persistence for eluxadoline and NPT model, and the impact of the modelled stopping rule on the high placebo response. In addition, the uncertainty in the difference in severity observed in the trial population and that of clinical practice could lead to the actual benefits of eluxadoline being lower than observed in the trials. As a result, the extrapolation of data beyond the treatment duration may be biasing the benefit in favour of eluxadoline, and the assumption of an ongoing benefit of eluxadoline after the treatment has been stopped could not be assessed in reanalyses.

At the submitted price of $4.51 per 100 mg daily, CDR estimated the ICUR for eluxadoline 100 mg to be between $105,829 and $121,004 per QALY compared with NPT. Price-reduction analyses using the CDR base cases indicate a price-reduction range of 70% to 80% and 50% to 60% may be required for eluxadoline to result in ICURs of $25,000 and $50,000 per QALY, respectively.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis of eluxadoline compared with no pharmacological therapy (NPT) as the current best supportive care for the treatment of patients with irritable bowel syndrome with diarrhea (IBS-D). The analysis used a cohort-based Markov model in which patients were followed over a five-year time horizon using four-week cycles based on the time points of data collection in the IBS-2001, IBS-3001, and IBS-3002 studies. The Markov model consisted of 17 health states, including 16 states based on levels of improvements in Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QoL) and pain scores and whether patients remain on treatment (continue) or discontinue:

- IBS-QoL: Four categories from a change from baseline in IBS-QoL score (less than 0; 0 or more to less than 14; 14 or more to less than 28; and 28 or more)
- Pain: Two categories from change from baselines in pain (less than 30% and 30% or more)
- Stopping treatment: Two categories comprising patients who did and did not stop treatment at four weeks.

The 17th state was death.

Patients enter the model in the IBS-QoL with change less than zero; pain score change < 30% health state as a continuer; and transition between health states based on changes in IBS-QoL and pain score. Discontinuers and continuers are followed separately in the model to allow for alternative assumptions regarding their expected costs and benefits.

Clinical effectiveness was informed by the IBS-2001, IBS-3001, and IBS-3002 studies.[2-4] Patient demographics at baseline were based on pooled data from the intention-to-treat population of the IBS-2001, IBS-3001, and IBS-3002 studies to align with the patient population entering the model.[2-4] For those who stopped treatment after four weeks (and therefore did not have ongoing measures of quality of life), the manufacturer carried forward its last observed quality of life for the rest of the model.[2] Persistence data were used to capture patients who discontinued eluxadoline or NPT after four weeks until the end of the model time horizon.[2] Persistence data on treatment with eluxadoline and placebo were collected until week 12 in IBS-2001, until week 26 in IBS-3002, and until week 52 in IBS-3001.[2] A Kaplan–Meier estimator provided pooled persistence from all three studies. Censors included those who completed the trial and those lost to follow-up. To model persistence over the model time horizon, the manufacturer fitted parametric distributions to the Kaplan–Meier data. The parametric distributions were selected by consideration of Akaike information criterion, Bayesian information criterion, and visual inspection of the fitted curves against the Kaplan–Meier data.[2] Based on this process, the log-normal distribution provided the best fit and was chosen for discontinuation of eluxadoline and NPT.[2] Patients stopping at four weeks due to inadequate relief reverted to their baseline utility, while patients stopping after four weeks based on persistence data received a utility based on the distribution across IBS-QoL/pain states at their last

observation prior to discontinuation, as well as 25% of the relative benefit with eluxadoline for the remainder of the model, despite having stopped treatment. This 25% relative benefit was not applied to the utility data directly but to the IBS-QoL/pain health state distribution of eluxadoline discontinuers (relative to the IBS-QoL/pain health state distribution for NPT discontinuers).[2]

Utility values were based on EuroQol 5-Dimensions questionnaire (EQ-5D) data from the IBS-2001 study (Dove et al.)[3] that were collected from patients at baseline, four weeks, eight weeks, and 12 weeks.[2] EQ-5D data were not collected in the IBS-3001 and IBS-3002 studies; only disease-specific quality-of-life measures were collected (IBS-QoL).[4] The manufacturer assumed the utilities to be constant over the five-year time horizon.[2] No disutilities due to adverse events were included in the model. Common adverse events with a greater than 5% difference between eluxadoline and placebo patients were nausea, vomiting, gastritis, abdominal pain, and constipation, all of which were mild to moderate in intensity and resolved with treatment discontinuation. The cost impact of these adverse events was captured in modelling the persistence on treatment.[2] No drug acquisition costs were applied to NPT in the model.[2] Both outcomes and costs accrued beyond the first year of the model were discounted at a rate of 1.5%, as per CADTH guidelines.[6] The analyses took the perspective of the publicly funded health care system in Canada in relation to costs and quality-of-life gains accrued by patients in relation to benefits.[2]

Manufacturer's Probabilistic Base Case

The manufacturer reported that eluxadoline (100 mg) resulted in total costs of $5,320 per patient compared with $3,442 for NPT, and total quality-adjusted life-years (QALYs) of 3.475 compared with 3.367 in NPT. This resulted in a probabilistic incremental cost-utility ratio (ICUR) of $17,384 per QALY for eluxadoline 100 mg compared with NPT (Table 2), with a 98% possibility of being cost-effective at a willingness-to-pay threshold of $25,000 per QALY.

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

	Total Costs ($)	Incremental Cost of Eluxadoline ($)	Total QALYs	Incremental QALYs of Eluxadoline	Incremental Cost per QALY
NPT	3,442	–	3.367	–	
Eluxadoline (100 mg)	5,320	1,878	3.475	0.108	$17,384

NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

The manufacturer conducted an alternative analysis in patients previously treated with loperamide.[2] This was a pre-specified prospective subgroup analysis in the IBS-3001 and IBS-3002 studies.[3,4] In this subgroup the manufacturer reported that eluxadoline (100 mg) resulted in total costs of $5,167 per patient compared with $3,446 for NPT, and QALYs of 3.441 compared with 3.354 in NPT. This resulted in a probabilistic ICUR of $19,742 per QALY for eluxadoline 100 mg compared with NPT (Table 3).

Table 3: Summary of Results of the Manufacturer's Probabilistic Alternative Analysis

	Total Costs ($)	Incremental Cost of Eluxadoline ($)	Total QALYs	Incremental QALYs of Eluxadoline	Incremental Cost per QALY
NPT	3,446	-	3.354	-	
Eluxadoline (100 mg)	5,167	1,721	3.441	0.087	$19,742

NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted probabilistic scenario analyses that varied the discount rate, time horizon, stopping rule, persistence curve modelling, resource utilization, and relative benefit. The ICURs for eluxadoline compared with NPT ranged from $5,238 per QALY gained for eluxadoline when persistence was modelled using a Gompertz distribution to $34,245 per QALY gained when the time horizon was shortened to 24 weeks. Changes in the assumed relative benefit following discontinuation had little effect on the cost-effectiveness of eluxadoline. The results were similarly robust using the alternative analysis in the prior-loperamide-use subgroup.

Limitations of Manufacturer's Submission

Use of Persistence Data for Eluxadoline and NPT

The manufacturer distinguished between the health statuses of those modelled to stop treatment at four weeks due to inadequate relief (early discontinuers) compared with late discontinuers; i.e., those modelled to discontinue based on the treatment persistence data observed in the trials. Persistence on treatment with eluxadoline and placebo data were collected until week 12 in IBS-2001, until week 26 in IBS-3002, and until week 52 in IBS-3001. The observed persistence trial data showed little difference between eluxadoline and NPT, but once extrapolated, showed a long-term persistence benefit for eluxadoline over NPT. Patients stopping at four weeks due to inadequate relief reverted to their baseline utility while patients stopping after four weeks based on persistence data received a utility based on the distribution across IBS-QoL/pain states at their last observation prior to discontinuation as well as 25% of the relative benefit with eluxadoline for the remainder of the model, despite having stopped treatment. The health state utilities in the trials were generally higher in the eluxadoline arm. Because fewer people on eluxadoline stopped treatment once the data were extrapolated, the magnitude of QALY gains in the eluxadoline arm increased. In addition, treatment persistence was modelled using separate parametric curves for placebo (used to represent NPT) and eluxadoline despite the lack of a comparative analysis that justifies a persistence benefit for eluxadoline over placebo. The impact of persistence on NPT is questionable in light of the uncertainty with how NPT effects were modelled in the analysis, and if the model correctly reflected the natural history of IBS-D then the need to account for persistence would not be required as patients continue alternative non-pharmacological treatments, even if adequate relief is not achieved. CADTH Common Drug Review (CDR) conducted a scenario analysis that set the persistence between the arms to equal using the log-normal distribution of eluxadoline. CDR also conducted an exploratory analysis that assumed all patients on NPT would persist on treatment beyond the early stopping point of four weeks (i.e., probability to

persist on NPT beyond week 4 was set at 100%). The results of the exploratory analysis are presented in Table 22.

Placebo Response in IBS-D Trial Patients

All three trials were placebo-controlled and had a high placebo response rate. Based on the manufacturer's modelled stopping rule, at four weeks with return to baseline utility, a larger proportion of patients stopped treatment at four weeks and returned to baseline utility in the NPT arm (50.1%) compared with the eluxadoline arm (38.7%). This drives a substantial increase in the estimated QALY gain for eluxadoline and effectively strips out the observed placebo response from 50.1% of the control arm, such that the modelled benefits for those continuing on eluxadoline are no longer fully controlled for placebo response. To assess the impact of the stopping rule and the placebo response, CDR conducted a scenario analysis that applied similar early stopping rates for both eluxadoline and NPT so that the modelled incremental costs and benefits of eluxadoline remain fully controlled for placebo response. CDR also conducted an exploratory analysis that assumed similar early stopping rates for eluxadoline and NPT as well assumed all patients on NPT would persist on treatment beyond the early stopping point of four weeks (i.e., probability to persist on NPT beyond week 4 was set at 100%). The results of the exploratory analysis are presented in Table 22.

Continuing Benefit After Treatment Discontinuation

The manufacturer applied a continuing benefit of eluxadoline (25% relative benefit) after stopping treatment and maintained it over the lifetime of the model (five years). No longitudinal data were presented to verify this benefit. A CDR scenario analysis excluded the ongoing 25% relative benefits in patients once they stopped eluxadoline treatment.

Use of Rome III Criteria in the Clinical Trials to Diagnose Patients With IBS-D

Based on feedback from the clinical expert, the Rome III or IV criteria could be difficult to apply in clinical practice based on the symptoms presented by the patients at assessment. Therefore, the patients presenting could have less-severe symptoms than patients enrolled in the trials. The difference between severity observed in the trial population and that seen in clinical practice could lead to the actual (absolute) benefits of eluxadoline being lower than observed in the trials.

The Primary Outcome in Trials Was a Composite Response of Pain and Stool Consistency

This outcome was not used in the economic model, which relied on IBS-QoL and pain as the measures of efficacy for eluxadoline. The clinical expert confirmed that IBS-QoL and pain measures are not common in clinical practice. The discrepancy in outcomes undermines the certainty regarding the true clinical efficacy of eluxadoline when used in practice.

Ongoing Scoping Costs

The manufacturer applied an annual cost of scoping (sigmoidoscopy, endoscopy, and colonoscopy) for the lifetime of the analysis (five years). Based on clinical expert opinion, no scoping is conducted if the patients were relatively young and presenting to a specialist for assessment. However, if the patients are at advanced age (with a higher risk for

colorectal cancer), then scoping is done in year 1, and possibly repeated after two or three years, but it is not done on an ongoing basis as modelled in the manufacturer's economic analysis. CDR conducted scenario analyses whereby the costs of scoping were either excluded completely or were excluded beyond the first year of the analysis.

Limitations With IBS-2001

The manufacturer included the clinical effectiveness inputs from IBS-2001, a phase II dose-finding, proof-of-concept study. The CDR clinical reviewer did not include IBS-2001, noting several limitations with the inclusion and exclusion criteria, the primary and secondary end points being subjective, and the use of a composite end point that utilizes a non-validated outcome (worst abdominal pain score). The inclusion of IBS-2001 conflicts with the manufacturer's objective of translating clinical outcomes of IBS-3001 and IBS-3002 within an economic evaluation. Further details are available in the CDR Clinical Review for eluxadoline in Appendix 5.

Alternate Analysis in the Prior-Loperamide-Use Subgroup Population

The manufacturer conducted an alternative analysis in the patient population with prior loperamide use. The analysis was based on a post hoc subgroup analysis that stratified patients who reported loperamide use in the year prior to study enrolment into those that reported adequate symptom control on loperamide use and those that did not.[7] The results of this subgroup analysis are uncertain due to several limitations identified with the subgroup analysis. First, the subgroup analysis was not pre-specified in the protocol section of the submitted clinical study reports of either IBS-3001 or IBS-3002. In addition, the identification of patients and the stratification based on potential recall of symptoms control in the past year was susceptible to recall bias. Finally, the subgroup analysis, with further stratification, is no longer considered representative of a randomized population and no baseline characteristics were reported to allow assessment of potential imbalances in group population. This subgroup was only assessed in CDR exploratory analyses (Appendix 5).

CADTH Common Drug Review Reanalyses

CDR identified uncertainty with several key parameters in the submitted model. Based on feedback from the clinical expert for this review, CDR conducted scenario analyses for a few parameters to assess the impact of the uncertainty on model results.

A. A scenario analysis was conducted that excluded the clinical effectiveness inputs from study IBS-2001, which was a phase II, proof-of-concept, dose-finding study, and not considered a pivotal study by Health Canada. Further details on the effects of including IBS-2001 are included in Appendix 5. CDR conducted the following exploratory analyses using the manufacturer's base- case analysis, which included the clinical effectiveness for eluxadoline from study IBS-2001. The data from IBS-2001 were also applied to the CDR base-case analyses, in which the persistence probabilities for NPT would be held constant at 100% (i.e., all patients beyond the week-4 stopping rule continue to use NPT throughout the model time horizon). In addition, the 25% relative benefit of eluxadoline maintained after discontinuation and ongoing scoping costs beyond year 1 were excluded from the CDR analyses. The results are summarized in Table 24.

CDR conducted the following exploratory analyses using the manufacturer's base-case analysis, which included the clinical effectiveness of eluxadoline from study IBS-2001. The data from IBS-2001 were also applied to the CDR base-case analyses in which the persistence probabilities for NPT would be held constant at 100% (i.e., all patients beyond the week-4 stopping rule continued to use NPT throughout the model time horizon) and the 25% relative benefit of eluxadoline maintained after discontinuation and ongoing scoping costs beyond year 1 were excluded. The results are summarized in Table 24.

B. The remaining CDR scenario analyses also excluded the inputs of IBS-2001.
C. An unjustified persistence benefit for eluxadoline over placebo was caused by modelling persistence using separate parametric curves for NPT and eluxadoline. Therefore, a scenario analysis that set the persistence between the arms to equal using the log-normal distribution of eluxadoline was conducted. (Table 14).
D. A scenario analysis that set the early stopping rates between the arms to equal using the early stopping rates for eluxadoline was conducted such that that the modelled incremental costs and benefits of eluxadoline remain fully controlled for placebo response (Table 15).
E. A scenario analysis excluded the ongoing 25% relative benefits in patients once they stopped eluxadoline treatment. (Table 16).
F. CDR conducted scenario analyses in which the costs of scoping were excluded beyond the first year of the analysis (Table 17) or were either excluded completely (Table 18).
G. CDR conducted multi-way scenario analyses based on excluding the clinical benefit after treatment was stopped, but not including:
    a) the ongoing costs of scoping beyond the first year of the analysis
    b) similar persistence data (full results presented in Table 19)
    c) similar early stopping rates (full results presented in Table 20)
    d) similar persistence data and early stopping rates (full results in Table 21).

Table 4: Summary of Results of the CDR Scenario Analyses

Scenario			Total Costs	Incremental Cost of Eluxadoline	QALYs	Incremental QALYs of Eluxadoline	Incremental Cost per QALY
Manufacturer's probabilistic base case		NPT	$3,442		3.367		$17,384
		Eluxadoline	$5,320	$1,878	3.475	0.108	
A	CDR probabilistic analysis: Exclusion of study IBS-2001	NPT	$3,443		3.366		
		Eluxadoline	$5,227	$1,784	3.461	0.095	$18,750
B	CDR probabilistic analysis: Use of similar persistence data for eluxadoline and NPT	NPT	$3,284		3.440		$92,641
		Eluxadoline	$5,227	$1,943	3.461	0.021	
C	CDR probabilistic analysis: Use similar early stopping rates for eluxadoline and NPT	NPT	$3,041		3.436		$85,671
		Eluxadoline	$5,228	$2,187	3.461	0.026	
D	CDR probabilistic analysis: excluding the ongoing 25% benefits after stopping	NPT	$3,443		3.366		$19,685
		Eluxadoline	$5,273	$1,829	3.459	0.093	
E1	CDR probabilistic analysis: Excluding the costs of scoping beyond the first year	NPT	$3,112		3.366		$19,219
		Eluxadoline	$4,940	$1,828	3.461	0.095	

Scenario			Total Costs	Incremental Cost of Eluxadoline	QALYs	Incremental QALYs of Eluxadoline	Incremental Cost per QALY
E2	CDR probabilistic analysis: Excluding the costs of scoping from model (year 1 and beyond)	NPT	$3,033		3.366		$19,427
		Eluxadoline	$4,874	$1,841	3.461	0.095	
F1	CDR multi-way probabilistic analysis (**Persistence**): A + B + D + E1	NPT	$2,969		3.440		**$105,829**
		Eluxadoline	$4,980	$2,011	3.459	0.019	
F2	CDR multi-way probabilistic analysis (**Stopping rates**): A + C + D + E1	NPT	$2,747		3.435		$94,053
		Eluxadoline	$4,981	$2,234	3.459	0.024	
F3	CDR multi-way probabilistic analysis (**Persistence + Stopping rates**): A + B + C + D + E1	NPT	$2,739		3.440		**$121,004**
		Eluxadoline	$4,980	$2,241	3.459	0.019	

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Price-reduction analyses were undertaken based on both CDR base-case analyses. The analyses varied the percentage reduction to illustrate the impact on the ICUR (Table 5). Price-reduction analyses using the CDR base cases indicate a price-reduction range of 70% to 80% and 50% to 60% may be required for eluxadoline to result in ICURs of $25,000 and $50,000 per QALY, respectively.

Table 5: CDR Reanalysis Price-Reduction Scenarios for Eluxadoline

	ICURs of Eluxadoline Versus NPT	
Price	**CDR Reanalysis (Scenario F1)**	**CDR Reanalysis (Scenario F3)**
	Excluding IBS-2001	Excluding IBS-2001
Submitted	$105,829	$121,004
10% reduction	$95,519	$105,575
20% reduction	$84,127	$94,825
30% reduction	$72,270	$84,746
40% reduction	$59,481	$71,249
50% reduction	$47,000	$59,095
60% reduction	$36,150	$48,553
70% reduction	$24,024	$36,086
80% reduction	$12,708	$25,133

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NPT = no pharmacological therapy.

Issues for Consideration

- Although the submitted evidence from the included studies suggests a beneficial effect of eluxadoline over placebo, only one-third of patients achieved responder status and the difference versus placebo was approximately 10%, suggesting an uncertain clinical benefit of treatment with eluxadoline. There is also a relatively small effect on abdominal pain; therefore, the value of this treatment in clinical practice is uncertain.
- The lack of active comparison is an evidence gap that has an impact on the ability to generalize the results into practice. Although loperamide is commonly used to manage symptoms of diarrhea in IBS-D patients and is recommended as first-line

pharmacotherapy for IBS-D patients as per the clinical expert, a lack of indirect evidence was found to help support an assessment of the comparative evidence of eluxadoline versus other commonly used drugs such as loperamide.

- The submitted model did not include all the possible symptoms associated with IBS as well as symptoms of any concurrent mental health disease and personality traits that are expected in IBS patients with treatment-resistant symptoms. The omission of such symptoms is not surprising because the associated clinical information is still not available.

Patient Input

Patient input for eluxadoline was provided by the Gastrointestinal Society patient group. According to the input received for this CDR submission, the patient group described IBS-D as a serious problem that significantly impairs quality of life. The input described the symptoms associated with IBS-D: frequent bowel movements, which can often be watery, along with bowel urgency, bloating, and abdominal pain. The health states of the economic model capture the impact of such symptoms on quality of life.

The patient group reported that there are treatments available for IBS-D. Diet and exercise, which includes eating regular well-balanced meals and snacks with high-fibre content (as set in Canada's Food Guide), and maintaining an adequate fluid intake are reported by the patient group to be able to help many, but not all, individuals with IBS-D manage diarrhea. Pelvic dysfunction physiotherapy, which may include bowel retraining, electrical stimulation, and posture correction, was also mentioned as a current therapy used for IBS-D that is helpful for some patients, but usually in combination with other treatments. Antidiarrheal medications that work by altering the muscle activity of the intestine to slow down transit time are also used. The submitted economic model compared eluxadoline with NPT and did not include antidiarrheal medications as comparators.

Conclusions

The key limitations of the submitted economic analysis as identified by CDR were the use of separate parametric curves to model treatment persistence for eluxadoline and NPT and the impact of the modelled stopping rule on the high placebo response. The uncertainty in the difference in severity between patients in the trial population and those in clinical practice could also lead to the actual benefits of eluxadoline being lower than observed in the trials and the extrapolation of data beyond the treatment duration may be biasing the benefit in favour of eluxadoline. The assumption of an ongoing benefit of eluxadoline after the treatment has been stopped is also unjustified.

At the submitted price of $4.51 per 100 mg daily, CDR estimated the ICUR for eluxadoline 100 mg to be between $105,829 and $121,004 per QALY compared with NPT. Price-reduction analyses using the CDR base cases indicate a price-reduction range of 70% to 80% and 50% to 60% may be required for eluxadoline to result in ICURs of $25,000 and $50,000 per QALY, respectively.

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 Comparisons for Treatments in Irritable Bowel Syndrome With Diarrhea

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Monthly Drug Cost ($)	Average Annual Drug Cost ($)
Eluxadoline (Viberzi)	**75 mg 100 mg**	**Tablet**	**2.2563[a]**	**100 mg taken orally twice daily with food[b]**	**135**	**1,620**
Anticholinergics (for abdominal pain)						
Dicyclomine hydrochloride (Bentylol)[c]	10 mg 20 mg	Tablet	0.1258[d] 0.2373[d]	10 to 20 mg three to four times daily. (maximum 160 mg/day)[e]	11 to 57	132 to 684
Hyoscine butylbromide (Buscopan)[c]	10 mg	Tablet	0.3368[d]	1 to 2 tablets per day (maximum of 6 tablets per day)[f]	10 to 61	120 to 732
Pinaverium bromide (Dicetel)	50 mg 100 mg	Tablet	0.3533[d] 0.6160[d]	50 mg three times a day (maximum total daily dose of 300 mg)[g]	32 to 55	384 to 660
Trimebutine maleate (Modulon, generic)	100 mg 200 mg	Tablet	0.2690 0.6275	Up to 600 mg daily in divided doses (200 mg three times daily)[h]	56	678
Antidiarrheals[c]						
Cholestyramine resin (Olestyr, generic)	4 g	Oral powder	0.5275	4 g orally every 12 hours [l]	32	384
Diphenoxylate hydrochloride/ Atropine sulphate (Lomotil)	2.5/0.025 mg	Tablet	0.5034	5 mg orally initially then 2.5 mg orally after each loose bowel movement (maximum 20 mg/day)[j]	30 to 120	360 to 1,440
Loperamide (Imodium, generic)	2 mg	Caplet	0.0952	2to4 mg oral as needed (maximum 12 mg/day) [i]	3 to 18	36 to 216

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Monthly Drug Cost ($)	Average Annual Drug Cost ($)
Tricyclic antidepressants (for abdominal pain)[c]						
Amitriptyline (Elavil, generic)	10 mg 25 mg 50 mg	Tablet	0.0435 0.0829 0.1540	25 to 100 mg orally at bedtime[i]	3 to 9	30 to 108
Desipramine (generics)	25 mg 50 mg 75 mg	Tablet	0.3880 0.6838 0.9093	25 to 100 mg orally at bedtime[i]	12 to 41	144 to 492

[a] Based on manufacturer's submission.

[b] From product monograph for eluxadoline (Viberzi).

[c] Not indicated for use in irritable bowel syndrome.

[d] Alberta Drug Benefit List (accessed March 22, 2018).[9]

[e] From product monograph for dicyclomine hydrochloride (Bentylol)[10]

[f] From product monograph for hyoscine butylbromide (Buscopan).[11]

[g] From product monograph for Pinaverium bromide (Dicetel).[12]

[h] From product monograph for Trimebutine maleate (Modulon).[13]

[i] E-Therapeutics (accessed March 22, 2018).[14]

[j] From product monograph for diphenoxylate hydrochloride and atropine sulphate (Lomotil).[15]

Source: Ontario Drug Benefit/Comparative Drug Index (effective March 22, 2018) unless otherwise noted.[8]

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Eluxadoline Relative to No Pharmacological Therapy?

Eluxadoline Versus NPT	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	$105,829 to $121,004 per QALY					

CE = cost-effectiveness; NA = not applicable; NPT = no pharmacological therapy (placebo); QALY = quality-adjusted life-year.

Note: Based on CADTH Common Drug Review reanalysis.

Appendix 3: Additional Information

Table 8: 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 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 HTA Reviews of Drug

The cost-effectiveness of eluxadoline (100 mg) has been assessed by the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC).[16,17] Based on the publicly available information, the economic analyses submitted to NICE and SMC appeared to be similar. However, only NICE recommended (with conditions) eluxadoline for use in patients with irritable bowel syndrome with diarrhea, while SMC did not recommend its use. The NICE and SMC reviews are presented in Table 10.

Table 10: Other Health Technology Assessment Findings

	NICE (August 2017)[16]	SMC (January 2018)[17]
Treatment	Eluxadoline 75 mg and 100 mg film-coated tablets	
Price	August 2017: The list price is £88.20 (C$143.65)[18] per pack of 56 tablets.[a]	January 2018: £1,147 (C$1,966)[19] annually (C$2.6932 per tablet)[b]
Similarities with CDR submission	Same comparator: no pharmacological therapy (NPT) Same model.	
Differences with CDR submission	Feedback on clinical practice (diagnostics, treatments, discontinuation, relative benefits) was based on a survey of Canadian gastroenterologists.	
Manufacturer's results	£5,576 (C$9,082)	£4,958 (C$8,499)
Issues noted by the review group	• The company applied costs of scoping (sigmoidoscopy, endoscopy and colonoscopy) as annual ongoing costs for the lifetime of model. The committee considered that these diagnostic procedures were unlikely after a diagnosis of IBS-D. • The committee was concerned with uncertainty about impact of any placebo effect and stopping rule. • The treatment duration data in trial showed little difference between eluxadoline and non-pharmacological treatment arms but, once extrapolated, showed fewer people on eluxadoline stopped treatment vs. no pharmacological therapy. • The heath-state utilities in trials were generally higher in eluxadoline arm. Because fewer people on eluxadoline stopped treatment once the data were extrapolated, the magnitude of benefit in eluxadoline arm was increased. • The plausibility of 25% of relative benefit of eluxadoline being maintained over the lifetime of the model (5 years) was uncertain, and no longitudinal data were presented to verify this benefit.	• Some uncertainty surrounding use of total change from baseline score in IBS-QoL and daily pain, given the primary outcomes were IBS-QoL and improvement in pain response. • Some uncertainty surrounding modelled treatment effect associated with eluxadoline arm. • A 25% benefit for patients discontinuing eluxadoline after 4 weeks was included. The benefit is applied to eluxadoline only. No data to support this assumption. • For extrapolation of persistence in the no-treatment arm, the Gompertz curve appeared to provide a better fit to the Kaplan–Meier data based on goodness-of-fit statistics. • Some uncertainty surrounding base-case utility values derived from short-term (12 week) phase II study data. • Based on a review of previously published resource use estimates within similar health technology assessments for IBS-constipation, resource-use estimates for inadequate responders (and subsequently no treatment) appear to be overestimated.

	NICE (August 2017)[16]	SMC (January 2018)[17]
Results of reanalyses by the review group	£12,049 (C$19,624)	None reported
Recommendation	Eluxadoline is recommended as an option for treating irritable bowel syndrome with diarrhea in adults, only if: • the condition has not responded to other pharmacological treatments (for example, • antimotility drugs, antispasmodics, tricyclic antidepressants) or • pharmacological treatments are contraindicated or not tolerated and • it is started in secondary care. Stop eluxadoline at 4 weeks if there is inadequate relief of the symptoms of irritable bowel syndrome with diarrhea.	Eluxadoline (Truberzi) is not recommended for use within NHS Scotland (the submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC).

CDR = CADTH Common Drug Review; IBS = irritable bowel syndrome; IBS-QoL = Irritable Bowel Syndrome Quality of Life questionnaire; NHS = National Health Service of the UK; NICE = National Institute for Health and Care Excellence; NPT = no pharmacological therapy; SMC = Scottish Medicines Consortium.

[a] Exchange rate (August 2017): £1 = C$1.6287.

[b] Exchange rate (January 2018): £1 = C$1.7141.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer used quality-of-life regression, the Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QoL) and pain scores to define the health states in the model. Treatment continuers and discontinuers were considered separate states, with different parameters associated with their use, to model the effects of discontinuation on both resource use and quality of life.

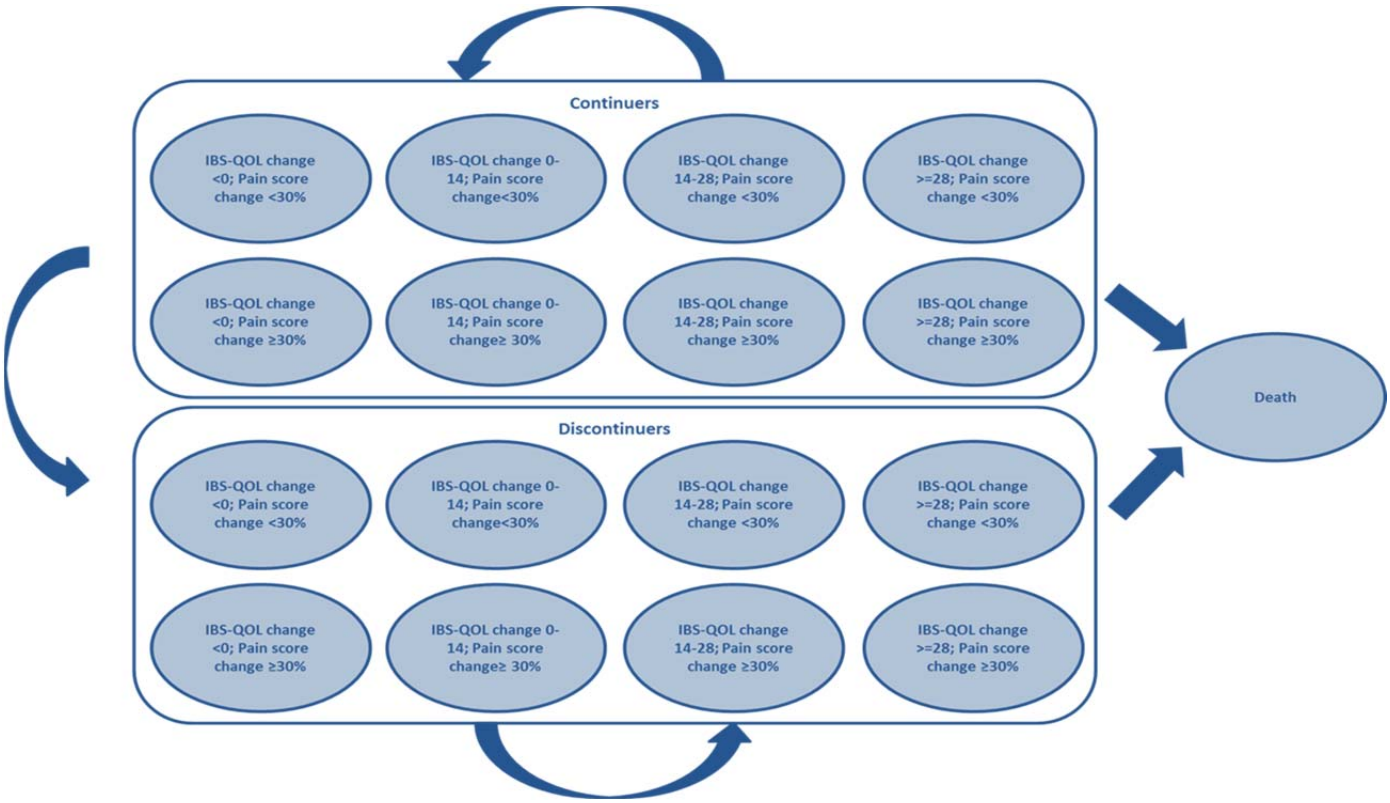
The Markov model consists of 17 health states based on levels of improvements in IBS-QoL and pain and whether patients remain on treatment (continuers) or discontinue (Figure 1):

- Continuers:
  - IBS-QoL 1 with pain not improved (PNI): IBS-QoL total score change < 0 from baseline and pain score improvement of < 30% from baseline
  - IBS-QoL 2 with PNI: IBS-QoL total score change ≥ 0 and < 14 from baseline and pain score improvement of < 30% from baseline
  - IBS-QoL 3 with PNI: IBS-QoL total score change ≥ 14 and < 28 from baseline and pain score improvement of < 30% from baseline
  - IBS-QoL 4 with PNI: IBS-QoL total score change ≥ 28 from baseline and pain score improvement of < 30% from baseline
  - IBS-QoL 1 with pain improved (PI): IBS-QoL total score change < 0 from baseline and pain score improvement of ≥ 30% from baseline
  - IBS-QoL 2 with PI: IBS-QoL total score change ≥ 0 and < 14 from baseline and pain score improvement of ≥ 30% from baseline
  - IBS-QoL 3 with PI: IBS-QoL total score change ≥ 14 and < 28 from baseline and pain score improvement of ≥ 30% from baseline
  - IBS-QoL 4 with PI: IBS-QoL total score change ≥ 28 from baseline and pain score improvement of ≥ 30% from baseline
- Discontinuers:
  - IBS-QoL 1 with PNI: IBS-QoL total score change < 0 from baseline and pain score improvement of < 30% from baseline
  - IBS-QoL 2 with PNI: IBS-QoL total score change ≥ 0 and < 14 from baseline and pain score improvement of < 30% from baseline
  - IBS-QoL 3 with PNI: IBS-QoL total score change ≥ 14 and < 28 from baseline and pain score improvement of < 30% from baseline
  - IBS-QoL 4 with PNI: IBS-QoL total score change ≥ 28 from baseline and pain score improvement of < 30% from baseline
  - IBS-QoL 1 with PI: IBS-QoL total score change < 0 from baseline and pain score improvement of ≥ 30% from baseline
  - IBS-QoL 2 with PI: IBS-QoL total score change ≥ 0 and < 14 from baseline and pain score improvement of ≥ 30% from baseline

- IBS-QoL 3 with PI: IBS-QoL total score change ≥ 14 and < 28 from baseline and pain score improvement of ≥ 30% from baseline
- IBS-QoL 4 with PI: IBS-QoL total score change ≥ 28 from baseline and pain score improvement of ≥ 30% from baseline

- Death.

Figure 1: Manufacturer's Markov Cohort Model



IBS-QOL = Irritable Bowel Syndrome Quality of Life questionnaire.
Source: Manufacturer pharmacoeconomic submission.[2]

The intervals assigned to the change in IBS-QoL from baseline were:

- IBS-QoL total score change < 0 from baseline to capture when patients reported an IBS-QoL score improvement of less than 0 points from baseline.
- IBS-QoL total score change ≥ 0 and < 14 from baseline to capture when patients reported an IBS-QoL score improvement of 0 points or more and less than 14 points from baseline.
- IBS-QoL total score change ≥ 14 and < 28 from baseline to capture when patients reported an IBS-QoL score improvement of 14 points or more and less than 28 points from baseline.
- IBS-QoL total score change ≥ 28 from baseline to capture when patients reported an IBS-QoL score improvement of 28 points or more from baseline.

The intervals assigned to the pain score improvement from baseline were aligned with the definitions used in the IBS-2001, IBS-3001 and IBS-3002 trials[3,4] and are as follows:

- Pain score improvement of ≥ 30% from baseline to capture when patients reported a pain score improvement of 30% or more from baseline.
- Pain score improvement of < 30% from baseline to capture when patients reported a pain score improvement of less than 30% from baseline.

The decision to stop any treatment at the four- to eight-weeks follow-up consultation was assumed to be based on a patient's perception of adequate relief as opposed to clinical measurements of disease severity used in trials. Therefore, the manufacturer used adequate relief to model treatment discontinuation. The definition of adequate relief was based on patient responses to the following question: "Over the past week, have you had adequate relief of your IBS symptoms?" once per week throughout the first 26 weeks of double-blind treatment. This was a pre-specified end point in the IBS-3001 and IBS-3002 clinical trials, and reflects how patients are assessed in clinical practice.[4]

Patients transition between the 17 health states as follows:

- Two cohorts, each comprising 1,000 patients with irritable bowel syndrome with diarrhea (IBS-D), enter the model in the IBS-QoL 1 with PNI health state as continuers based on the baseline demographics of patients in the IBS-2001, IBS-3001 and IBS-3002 studies. One cohort receives eluxadoline while the other receives no pharmacological therapy (NPT).
- For each cohort:
  - Patients that die, due to Canadian general population all-cause mortality rates, transition to the "Dead" state.
  - Alive patients transition between the IBS-QoL/pain continuer health states based on treatment-specific transition matrices.
  - Within the IBS-QoL/pain continuer health states patients either remain as continuers on treatment or transition to become discontinuers based on a stopping rule at four (or eight) weeks and persistence parametric curves beyond 26 weeks.
  - A mid-cycle correction is applied.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	**IBS-2001 study** (Dove et al. [2013]) enrolled patients with a diagnosis of IBS by Rome III criteria with a subtype of diarrhea who met screening and baseline criteria for pain (daily pain scores of ≥ 3.0 on a 0- to 10-point scale) and stool consistency (Bristol stool scale [BSS] score of ≥ 5.5 over the past week). IBS-QoL, IBS adequate relief (IBS-AR) and EQ-5D were collected for eluxadoline and placebo patients at baseline, 4 weeks, 8 weeks and 12 weeks.[3] **IBS-3001 study** (Lembo et al. [2016]) enrolled patients with a diagnosis of IBS by the Rome III criteria with a subtype of diarrhea who met screening and baseline criteria for pain (average of daily worst abdominal pain scores > 3.0 [scale 0-10] in the week prior to randomization); stool consistency (average BSS score of ≥ 5.5 [scale 1–7] and at least 5 days with a BSS score ≥ 5 the week prior to randomization); and IBS-D global symptom (IBS-D score ≥ 2.0 [scale 0–4] the week prior to randomization). IBS-QoL was collected at baseline, 4 weeks, 8 weeks, 12 weeks, 18 weeks, 26 weeks, 36 weeks, 44 weeks and 52 weeks. IBS-AR was collected weekly until 26 weeks.[4] **IBS-3002 study** (Lembo et al. [2016]) enrolled patients with a diagnosis of IBS with a subtype of diarrhea using the same criteria as the IBS-3001 study. IBS-QoL was collected at baseline, 4 weeks, 8 weeks, 12 weeks, 18 weeks, 26 weeks and 30 weeks. IBS-AR was collected weekly until 26 weeks.[4]	Patients were excluded if they were receiving antidiarrheal or antispasmodic therapies at baseline. Patients receiving antidepressants were eligible to participate in the study provided that dosing had been stable for 12 weeks or longer before enrolment.
Natural history	Patient demographics at baseline were based on pooled data from the ITT population of the IBS-2001, IBS-3001, and IBS-3002 studies to align with the patient population entering the model.[3,4]	Acceptable.
Mortality	Mortality was based on all-cause mortality rates stratified by age and gender presented in life tables by Statistics Canada.[20]	Acceptable.
Utilities	Based on EQ-5D data collected from IBS-2001.[3]	Acceptable. EQ-5D data were not collected in the IBS-3001 and IBS-3002; only disease-specific quality of life measures were collected (IBS-QoL).[4]
Resource use	Annual resource use estimates identified from the IBS-D secondary care questionnaire with Canadian physicians was used as the base-case analysis. These estimates were targeted at IBS-D specifically and addressed questions specific to the decision problem of eluxadoline.[2]	Acceptable.
Adverse events	No disutilities due to adverse events were included in the model as the clinical trial data have shown that the overall incidence of adverse events is similar across treatment groups	Acceptable.
Costs		
Drug	Drug costs for eluxadoline were calculated based on the cost of $135.3780 per package (60-tablet bottle) of either 75 mg or 100 mg strengths as provided by the manufacturer.[2]	Acceptable. The price for eluxadoline 100 mg per day is $4.51. This was multiplied by 28 to give a 4-week cycle cost of $126.35.
Event	Unit costs were sourced from: the Ontario Ministry of Health and Long-Term Care Schedule of Physician Benefits and Schedule of Laboratory Services, and the Canadian Institute for Health Information Case Mix Group Patient Cost Estimator.[21-23]	Acceptable.

BSS = Bristol stool scale; EQ-5D = EuroQol 5-Dimensions questionnaire; IBS-AR = adequate relief of irritable bowel syndrome; IBS-D = irritable bowel syndrome with diarrhea; IBS-QoL = Irritable Bowel Syndrome Quality of Life questionnaire; ITT = intention to treat.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Patients are assumed to enter the model in the IBS-QoL 1 with PNI health state as continuers; that is, patients receiving treatment with an IBS-QoL total score change of < 0 points from baseline and pain score improvement of < 30% from baseline.	Uncertain.
Utilities were assumed to be constant over the five-year time horizon.	Uncertain. Based on clinical expert feedback, the patients reported quality of life may change with IBS-D frequently over time, especially if they are not stabilized on a treatment or lifestyle plan.
At week 4, the eluxadoline compliance rate was assumed to be 100% to account for the fact that a 4-week pack size would be prescribed at baseline.	Uncertain. Based on clinical expert feedback, patients are likely to be compliant at first as they are eager to achieve the treatment effect. If the clinical effect is not reached soon after they start, the patients will report inadequate relief and then possibly discontinue therapy.
The cost of eluxadoline was calculated based on the observed data from IBS-2001, IBS-3001, and IBS-3002. The 4-week cycle cost was adjusted for compliance and persistence to preserve the ITT principle in evaluating treatment effectiveness based on IBS-2001, IBS-3001 and IBS-3002.	Appropriate.
Patients stopping at 4 weeks due to inadequate relief revert to their baseline utility.	Appropriate.
Patients discontinuing after 4 weeks receive half the additional benefit as estimated by IBS experts (i.e., half of 50% = 25% relative benefit).	Not appropriate. No longitudinal data were presented to verify this benefit.
Upon stopping treatment, patients incurred no treatment costs and incurred disease-related costs based on the proportion adequately/inadequately relieved at their last observation prior to discontinuation.	Appropriate.

IBS-D = irritable bowel syndrome with diarrhea; IBS-QoL = Irritable Bowel Syndrome Quality of Life questionnaire; ITT = intention-to-treat; PNI = pain not improved.

Manufacturer's Deterministic Results

Results of the manufacturer's base-case deterministic analysis are presented in Table 13.

Table 13: Results of the Manufacturer's Deterministic Analysis

Treatment	Treatment Costs	Disease-Related Costs	Total Costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYGs	Incremental QALYs	Incremental Cost per QALY
NPT	0	$3,450	$3,450	4.833	3.373				
Eluxadoline (100 mg)	$2,308	$2,984	$5,292	4.833	3.479	$1,842	0.000	0.106	$17,349

LYG = life-year gained; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

CADTH Common Drug Review Reanalyses – Detailed Results

CADTH Common Drug Review (CDR) undertook the following probabilistic scenario analyses on the manufacturer's base case.

Use of persistence data for eluxadoline and NPT. Treatment persistence was modelled using separate parametric curves for placebo (used to represent NPT) and eluxadoline despite the lack of a comparative analysis that justifies a persistence benefit for eluxadoline over placebo. CDR conducted a scenario analysis that set the persistence between the arms to equal using the log-normal distribution of eluxadoline by selecting and copying the persistence probability per cycle values for eluxadoline and then pasting them as the new values for placebo before running a probabilistic sensitivity analysis using a sample size of 5,000. The results of the CDR reanalysis are summarized in Table 14.

Table 14: CDR Scenario Analysis – Equal Persistence for Eluxadoline and NPT

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
NPT	$3,284		3.440		
Eluxadoline	$5,227	$1,943	3.461	0.021	$92,641

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Placebo response and stopping rule in IBS-D trial patients. To assess the impact of the stopping rule and the placebo response, CDR conducted a scenario analysis that applied similar early stopping rates for both eluxadoline and NPT so that the modelled incremental costs and benefits of eluxadoline remain fully controlled for placebo response. The results of the CDR reanalysis are summarized in Table 15.

Table 15: CDR Scenario Analysis – Controlling for Placebo Response and Similar Early Stopping Rates for Eluxadoline and NPT

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
NPT	$3,041		3.436		
Eluxadoline	$5,228	$2,187	3.461	0.026	$85,671

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Exclude the 25% relative benefits of eluxadoline maintained after discontinuation. The plausibility of 25% of the relative benefit of eluxadoline being maintained over the lifetime of the model (five years) was uncertain, and no longitudinal data were presented to support this assumption by the manufacturer based on clinical opinion. The results for eluxadoline slightly increased to $19,685 per QALY compared with NPT. The results of the CDR reanalysis are summarized in Table 16.

Table 16: CDR Scenario Analysis – Excluding 25% Relative Benefits on Eluxadoline After Discontinuation

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
NPT	$3,443		3.366		
Eluxadoline	$5,273	$1,829	3.459	0.093	$19,685

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Costs of scoping. Ongoing scoping (sigmoidoscopy, endoscopy and colonoscopy) costs should not be included in the model: the manufacturer's economic analysis applied costs of scoping as an annual ongoing cost for the model's time horizon (five years). According to clinical expert feedback, diagnostic procedures after the diagnosis of IBS-D has been made were unlikely. A CDR scenario analysis excluded the ongoing scoping costs beyond year 1; the results are summarized in Table 17. A more conservative CDR scenario analysis was conducted excluding the ongoing costs for scoping completely; the results are summarized in Table 18.

Table 17: CDR Scenario Analysis – Excluding Ongoing Scoping Costs Beyond Year 1

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
NPT	3,112		3.366		
Eluxadoline	4,940	1,828	3.461	0.095	$19,219

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Table 18: CDR Scenario Analysis – Excluding Ongoing Scoping Costs

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
NPT	3,033		3.366		
Eluxadoline	4,874	1,841	3.461	0.095	$19,427

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Multi-way scenario analyses. CDR conducted a multi-way scenario analysis that set the persistence between the arms to equal using the log-normal distribution of eluxadoline, excluded the 25% relative benefit of eluxadoline maintained after discontinuation, and excluded ongoing scoping costs beyond year 1. The results of the CDR reanalysis are summarized in Table 19.

Table 19: Summary of Results of CDR Multi-Way Scenario Analysis – Similar Persistence Eluxadoline and NPT

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
NPT	$2,969		3.440		
Eluxadoline	$4,980	$2,011	3.459	0.019	$105,829

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

CDR conducted a multi-way scenario analysis that applied similar early stopping rates for both eluxadoline and NPT, excluded the 25% relative benefit of eluxadoline maintained after discontinuation, and excluded ongoing scoping costs beyond year 1. The results of the CDR reanalysis are summarized in Table 20.

Table 20: Summary of Results of CDR Multi-Way Scenario Analysis – Placebo Response and Early Stopping Rates for Eluxadoline and NPT

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
NPT	$2,747		3.435		
Eluxadoline	$4,981	$2,234	3.459	0.024	$94,053

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life year.

CDR conducted a multi-way scenario analysis that applied similar values for persistence data and early stopping rates for both eluxadoline and NPT, excluded the 25% relative benefit of eluxadoline maintained after discontinuation, and excluded ongoing scoping costs beyond year 1. The results are summarized in Table 21.

Table 21: Summary of Results of CDR Multi-Way Scenario Analysis – Similar Persistence Data and Early Stopping Rates for Eluxadoline and NPT

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALY	Incremental Cost per QALY
NPT	2,739		3.440		
Eluxadoline	4,980	2,241	3.459	0.019	$121,004

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

CDR conducted exploratory analyses on both CDR base-case analyses in which the persistence probabilities for NPT were held constant at 100% (i.e., all patients beyond the week-4 stopping rule continue to use NPT throughout the model time horizon) and the 25% relative benefit of eluxadoline maintained after discontinuation as well as ongoing scoping costs beyond year 1 were excluded. The results are summarized in Table 22.

Table 22: Summary of Results of the CDR Multi-Way Exploratory Analyses – Persistence Data and Early Stopping Rates for Eluxadoline and NPT

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
Continuous persistence beyond 4 weeks (i.e., 100%) for NPT					
NPT	$2,021		3.774		
Eluxadoline	$4,979	$2,958	3.459	−0.315	Dominated
Continuous persistence beyond 4 weeks (i.e., 100%) and similar early stopping rates for NPT					
NPT	$1,502		3.774		
Eluxadoline	$4,980	$3,477	3.459	−0.315	Dominated

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Loperamide-experienced subgroup. CDR conducted exploratory analyses in the subgroup of patients with prior loperamide use. The analyses applied similar values for persistence data and early stopping rates for both eluxadoline and NPT, excluded the 25% relative benefit of eluxadoline maintained after discontinuation, and excluded ongoing scoping costs beyond year 1. The results are summarized in Table 23.

Table 23: CDR Multi-Way Exploratory Analyses in Patients with Prior Loperamide Use

Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
Similar persistence beyond 4 weeks for eluxadoline and NPT					
NPT	$2,969		3.428		
Eluxadoline	$4,928	$1,959	3.435	0.007	$271,431
Similar persistence and early stopping rates beyond 4 weeks for eluxadoline and NPT					
NPT	$2,738		3.428		
Eluxadoline	$4,927	$2,189	3.435	0.007	$291,918

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Price-reduction analyses were undertaken based on both CDR exploratory analyses in patients with prior loperamide use. Price- reduction analyses indicate a price-reduction range of 75% to 86% may be required for eluxadoline to result in an incremental cost-utility ratio (ICUR) of $50,000 per QALY in patients with prior loperamide use.

Inclusion of Study IBS-2001 for clinical effectiveness. CDR conducted the following exploratory analyses using the manufacturer's base-case analysis, which included the clinical effectiveness of eluxadoline from study IBS-2001. The data from IBS-2001 were also applied to the CDR base-case analyses in which the persistence probabilities for NPT would be held constant at 100% (i.e., all patients beyond the week-4 stopping rule continued to use NPT throughout the model time horizon) and the 25% relative benefit of eluxadoline maintained after discontinuation and ongoing scoping costs beyond year 1 were excluded. The results are summarized in Table 24.

Table 24: CDR Reanalyses Including IBS-2001 for Clinical Effectiveness

Scenario	Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
A	Equal persistence for eluxadoline and NPT					
	NPT	$3,269		3.449		
	Eluxadoline	$5,320	$2,051	3.475	0.027	$77,270
B	Controlling for placebo response and similar early stopping rates for eluxadoline and NPT					
	NPT	$2,995		3.446		
	Eluxadoline	$5,321	$2,326	3.475	0.029	$80,816
C	Excluding 25% relative benefits on eluxadoline after discontinuation					
	NPT	$3,442		3.367		
	Eluxadoline	$5,367	$1,924	3.473	0.106	$18,137
D	Excluding ongoing scoping costs beyond year 1					
	NPT	$3,111		3.367		
	Eluxadoline	$5,036	$1,924	3.475	0.108	$17,789

Scenario	Treatment	Total Costs	Incremental Cost	Total QALYs	Incremental QALYs	Incremental Cost per QALY
E	Excluding ongoing scoping costs					
	NPT	$3,032		3.367		
	Eluxadoline	$4,975	$1,943	3.475	0.108	$17,960
F	Multi-way analysis – similar persistence eluxadoline and NPT					
	NPT	$2,955		3.448		
	Eluxadoline	$5,077	$2,122	3.473	0.025	$84,387
G	Multi-way analysis – placebo response and early stopping rates for eluxadoline and NPT					
	NPT	$2,705		3.446		
	Eluxadoline	$5,076	$2,371	3.473	0.027	$87,294
H	Multi-way analysis – similar persistence data and early stopping rates for eluxadoline and NPT					
	NPT	$2,712		3.448		
	Eluxadoline	$5,077	$2,365	3.473	0.025	$95,895

CDR = CADTH Common Drug Review; NPT = no pharmacological therapy; QALY = quality-adjusted life-year.

Price-reduction analyses were also undertaken based on both CDR base-case analyses that included the clinical effectiveness of eluxadoline from study IBS-2001. The analyses varied the percentage reduction to illustrate the impact on the ICUR (Table 25). Price-reduction analyses using the CDR base cases indicate a price-reduction range of 60% to 70% and 40% to 50% may be required for eluxadoline to result in ICURs of $25,000 and $50,000 per QALY, respectively.

Table 25: CDR Price-Reduction Reanalyses Including IBS-2001 for Clinical Effectiveness

	ICURs of Eluxadoline Versus NPT	
Price	**CDR reanalysis (Scenario F)**	**CDR reanalysis (Scenario H)**
	Including IBS-2001	Including IBS-2001
Submitted	$84,387	$95,895
10% reduction	$77,002	$84,703
20% reduction	$67,991	$75,544
30% reduction	$55,649	$67,829
40% reduction	$47,294	$56,619
50% reduction	$37,984	$48,306
60% reduction	Not performed	$38,486
70% reduction	Not performed	$28,644

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NPT = no pharmacological therapy.

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