CADTH

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ELUXADOLINE (VIBERZI — ALLERGAN PHARMA CO.)
Indication: Irritable bowel syndrome with diarrhea

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that eluxadoline not be reimbursed for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

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The CADTH Canadian Drug Expert Committee (CDEC) recommends that eluxadoline not be reimbursed for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

Reasons for the Recommendation

1. The results of two phase III, double-blind, randomized, placebo-controlled, parallel-group, trials (IBS-3001, N = 1,281; and IBS-3002, N = 1,146) demonstrated a statistically significant improvement in the primary composite outcome (daily pain response and daily stool consistency response) for eluxadoline (75 mg twice daily and 100 mg twice daily) compared with placebo between baseline and 12 and 26 weeks. However, only approximately one-third of patients in the eluxadoline treatment arm were considered responders for this composite end point, which was driven primarily by stool consistency responders. There were no statistically significant differences between eluxadoline and placebo for the percentage of daily pain responders in either study between baseline and 12 or 26 weeks. Quality of life comparisons using the least squares mean difference in irritable bowel syndrome quality of life (IBS-QoL) questionnaire results showed a statistically significant difference between the active groups and placebo except at week 26 and week 30 in the 100 mg eluxadoline arm in IBS-3002. However, there was no clear benefit of eluxadoline on patients' quality of life based on the IBS-QoL questionnaire when measured as the percentage of patients who met the pre-specified minimal clinically important difference (MCID) threshold of a 14-point difference, except in the IBS-3001 eluxadoline 100 mg group at week 52. The lack of control for multiple statistical testing for outcomes other than the primary composite outcome and the high percentage of patients discontinuing from the studies further limit the ability to interpret the findings.
2. Eluxadoline use was associated with higher rates of withdrawals due to adverse events compared with placebo in both trials. Pancreatitis was reported in seven patients, all of whom were in the eluxadoline treatment groups.
3. No direct or indirect comparative evidence is available to assess the clinical benefit of eluxadoline versus other pharmacological agents commonly used to treat IBS-D.

Discussion Points

- The committee recognized that eluxadoline is the first Health Canada–approved pharmacological agent for use in patients with IBS-D. However, several other agents (e.g., antidiarrheals, tricyclic antidepressants, and antispasmotics) are commonly used in clinical practice to manage symptoms of diarrhea in patients with IBS-D. The comparative clinical effectiveness of eluxadoline versus other commonly used agents, such as loperamide, is unknown.

Background

Eluxadoline has a Health Canada–approved indication for the treatment of IBS-D in adults. Eluxadoline is a mixed mu opioid receptor agonist and delta opioid receptor antagonist. It is available as an oral tablet and the Health Canada–approved dosage is 100 mg twice daily. A reduced dose of 75 mg is also approved and recommended for geriatric patients or those who cannot tolerate the 100 mg dose.

Summary of CDEC Considerations

The committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of a phase III randomized controlled trial of eluxadoline and a critique of the manufacturer's pharmacoeconomic evaluation.

The committee also considered input from a clinical expert with experience in treating patients with IBS-D, as well as patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

One patient group, the Gastrointestinal Society, provided input for this submission. Patient perspectives were obtained from printed sources, collective feedback from patients associated with the society who suffer from diarrhea-predominant IBS, information written by physicians for their publications (newsletters, pamphlets, and websites), and responses from an online survey (with approximately 3,000 respondents) of patients with IBS. The following is a summary of key input from the perspective of the patient group:

- Individuals with IBS-D report that one of the most uncomfortable aspects of IBS-D is not knowing when symptoms might strike. Consequently, many individuals with IBS-D avoid social gatherings and other outings, which can lead them to feel embarrassed, self-conscious, and ashamed, and significantly impairing their quality of life.
- While some treatments are available for IBS-D, including diet and exercise, physiotherapy, and anti-diarrheal medications, many patients do not see improvements using available treatment options.
- Patients have expressed that these treatments become ineffective over time or do not work, and that the affordability of treatments and products is an issue.
- Patients expect eluxadoline to provide an additional treatment option, considering that IBS is a highly individualized disorder.

Clinical Trials

The systematic review included two phase III, double-blind, randomized, placebo-controlled, parallel-group trials (IBS-3001, N = 1,281; and IBS-3002, N = 1,146) of patients with IBS-D, as diagnosed per Rome III criteria.

Patients were randomized in a 1:1:1 ratio to 75 mg twice-daily eluxadoline, 100 mg twice-daily eluxadoline, and placebo groups. The primary outcome of both studies was a composite of worst abdominal pain score and stool consistency responders during an interval of one to 12 weeks (FDA end point requirement) or one to 26 weeks (European Medicines Agency end point requirement). Both studies were identical in design except that IBS-3001 included an additional 26 weeks of double-blind treatment with a subsequent two weeks of follow-up, while IBS-3002 included an additional four weeks of a single-blinded withdrawal period. All efficacy outcomes were reported at either 12 weeks or 26 weeks. IBS-QoL responses were reported at the end visit of each of the studies. Limitations of the studies include the lack of active comparators, a high percentage of patients discontinuing in both studies, a primary outcome not commonly used in clinical practice, and a lack of adjustment for multiple statistical testing.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- Stool consistency (part of the primary outcome in both trials): a stool consistency responder was defined in the trials as a patient who recorded, on at least half the days over a 12-week or a 26-week interval, a daily stool consistency score of less than 5 using the Bristol stool scale tool or recorded absence of bowel movement when accompanied by worst abdominal pain of 30% or less compared with baseline.
- Pain intensity (part of the primary outcome in both trials): a pain responder was defined in the trials as a patient who recorded in the diary that their worst abdominal pain score in the past 24 hours improved by 30% or more compared with baseline, on at least half the days over a 12-week or a 26-week interval.
- Relief of IBS symptoms, including: abdominal discomfort (secondary outcome in the trials, measured in the trials as a patient who recorded a weekly response of “Yes” to adequate relief of their IBS symptoms for at least half of the total weeks during the 12- or 26-week intervals); urgency (secondary outcome in the trials, patient-reported number of urgency episodes per day); and frequency (secondary outcome in the trials, measured as a patient-reported number of bowel movements per day).

- Health-related quality of life: assessed using the IBS-QoL questionnaire, which consists of 34 questions that are answered by patients according to a five-point Likert scale, with 1 corresponding to having the least impact on quality of life, and 5 as having the greatest impact. An IBS-QoL responder was defined as a patient who achieved an improvement of at least 14 points in total score from baseline to the recorded visit (12 or 26 weeks) on at least half the days over a 12-week or a 26-week interval).
- Adverse events, severe adverse events, and withdrawals due to adverse events.

The primary outcome of both studies was a composite of worst abdominal pain score and stool consistency responders during the interval of one to 12 weeks (FDA end point requirement) or one to 26 weeks (European Medicines Agency end point requirement). A responder was defined as a patient who achieved a responder status for both worst abdominal pain and stool consistency. For each component, the patient had to have reported an improvement of 30% or more compared with pre-screening on 50% or more of the days in the interval of interest.

Efficacy

In IBS-3001, 23.9% of patients in the 75 mg eluxadoline group and 25.1% in the 100 mg eluxadoline group achieved responder status in the 12-week interval compared with 17.1% in the placebo group (6.8% and 8.0% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively), with the differences between groups being statistically significant. No calculation of confidence intervals (CIs) was available. For the same 12-week interval in IBS-3002, there were higher percentages of responders in the eluxadoline groups: 28.9% in the 75 mg group, 29.6% in the 100 mg group, and 16.2% in the placebo group, also with statistically significant differences compared with placebo (12.7% and 13.4% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively). On the time interval of one to 26 weeks, in IBS-3001, 23.4% of patients in the 75 mg eluxadoline group and 29.3% in the 100 mg eluxadoline group achieved responder status compared with 19.0% responders in the placebo group (4.4% and 10.0% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively), with the differences between the 75 mg eluxadoline group and placebo group not achieving statistical significance and the difference between the 100 mg eluxadoline group and placebo group achieving statistical significance. No calculation of CIs was available. For the same interval of 26 weeks in IBS-3002, there were higher percentages of responders in the active eluxadoline groups; 30.4% in the 75 mg group, 32.7% in the 100 mg group, and 20.2% in the placebo group, also with statistically significant differences compared with placebo (10.2% and 12.5% differences in the 75 mg eluxadoline group and the 100 mg eluxadoline group versus placebo, respectively).

A breakdown of the primary outcome to its components was reported in the studies as secondary outcomes. The worst abdominal pain results did not show any statistically significant differences between eluxadoline groups and placebo groups in either study or the pooled results; specifically, at the 12-week interval, IBS-3001 reported 42.4% pain responders in the 75 mg eluxadoline group, 43.2% pain responders in the 100 mg eluxadoline group, and a 39.6% responders in the placebo group, while IBS-3002 reported 48.0% responders in the 75 mg eluxadoline group, 51.0% responders in the 100 mg eluxadoline group, and 45.3% responders in the placebo group. During the 26-week interval, IBS-3001 reported 45.2% pain responders in the 75 mg eluxadoline group, 46.5% pain responders in the 100 mg eluxadoline group, and a 43.3% responders in the placebo group, while IBS-3002 reported 47.5% responders in the 75 mg eluxadoline group, 50.0% responders in the 100 mg eluxadoline group, and 44.8% responders in the placebo group. The stool consistency results show statistically significant differences between the eluxadoline groups and placebo at all time points and across both studies; specifically, at the 12-week interval, IBS-3001 reported 30.0% responders in the 75 mg eluxadoline group, 34.3% responders in the 100 mg eluxadoline group, and a 22.0% responders in the placebo group, while IBS-3002 reported 37.0% responders in the 75 mg eluxadoline group, 35.6% responders in the 100 mg eluxadoline group, and 20.9% responders in the placebo group. During the 26-week interval, IBS-3001 reported 28.1% responders in the 75 mg eluxadoline group, 34.0% responders in the 100 mg eluxadoline group, and a 24.1% responders in the placebo group, while IBS-3002 reported 34.4% responders in the 75 mg eluxadoline group, 39.8% responders in the 100 mg eluxadoline group, and 23.6% responders in the placebo group.

Other outcomes of relevance to this CDR review include bowel movement frequency, abdominal discomfort score, urgency episodes, and IBS-QoL total-score responders. All of these outcomes were reported as secondary outcomes in both studies with no adjustment for multiple testing. Bowel movement frequency shows a [redacted] versus placebo [redacted]. Specifically, at week 12, the risk ratios of bowel movement frequency in IBS-3001 were [redacted]

[redacted] in the comparisons between the 75 mg eluxadoline group and placebo, and between the 100 mg eluxadoline group and placebo, respectively. The risk ratios of bowel frequency in IBS-3002 at the same end point were [redacted] in the comparisons between the 75 mg eluxadoline group and placebo, and between the 100 mg eluxadoline group and placebo, respectively. [redacted] results were observed at the 26-week end point. Abdominal discomfort scores also show a [redacted]. Similar results were observed in the number of urgency episodes.

Health-related quality of life as measured using the IBS-QoL questionnaire was analyzed in two ways: the least squares mean difference of the total score between the eluxadoline groups and the placebo groups, and the percentage of responders using the MCID value of a 14-point difference. Overall, comparisons using the least squares mean difference showed statistically significant differences between the active groups and placebo except at week 26 and week 30 in the 100 mg eluxadoline arm in IBS-3002. However, when using the MCID definition to determine responders, no statistically significant differences were found in either study, except in the eluxadoline 100 mg group at week 52 in IBS-3001.

Harms (Safety and Tolerability)

In IBS-3001, a numerically higher proportion of patients had at least one serious adverse event with eluxadoline compared with placebo (5.8% in the 75 mg treated arm, 5.6% in the 100 mg treated arm, and 3.7% in the placebo arm).

In IBS-3002, a numerically similar proportion of patients had at least one serious adverse event with eluxadoline compared with placebo (2.4% in the 75 mg treated arm, 3.7% in the 100 mg treated arm, and 2.1% in the placebo arm).

Overall adverse events were numerically higher in the 75 mg eluxadoline arm in IBS-3001 (60.5%) when compared with the 100 mg arm (55.3%) and placebo (55.5%). While both active arms had a similar overall proportion of patients with at least one adverse event (59.9% in the 75 mg arm and 61.8% in the 100 mg arm), these were numerically higher than the placebo group (55.9%).

Cost and Cost-Effectiveness

Eluxadoline is indicated for the treatment of IBS-D. The manufacturer submitted a price of $2.26 per tablet for both the 75 mg and 100 mg strengths ($4.51 per day). The average annual cost for eluxadoline is $1,620 per patient.

The manufacturer submitted a cost-utility analysis from the perspective of the publicly funded health care system in Canada in which eluxadoline was compared with no pharmacological therapy (NPT) for the treatment of patients with IBS-D. 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, IBS-3001, and IBS-3002 studies. For patients who stopped treatment after four weeks, the manufacturer carried forward the person's last observed quality of life for the rest of the model, and used persistence data to capture patients that discontinue eluxadoline or NPT after four weeks until the end of the model time horizon. A Kaplan–Meier estimator provided pooled persistence estimates from all three studies. Patients who discontinued eluxadoline were assumed to maintain 25% of the relative benefit for the remainder of the model, despite having stopped treatment. The manufacturer reported that eluxadoline 100 mg is associated with an incremental cost per quality-adjusted life-year (QALY) of $17,384 compared with NPT.

CDR identified the following key limitations with the manufacturer's submitted economic analysis:

- The observed persistence with treatment in clinical trials shows little difference between eluxadoline and NPT. When persistence was extrapolated, fewer people receiving eluxadoline stopped treatment compared with NPT, resulting in QALY gains for patients in eluxadoline that may be overestimated.
- Treatment persistence was modelled using separate parametric curves for NPT (based on placebo) and eluxadoline despite the lack of a comparative analysis that justifies a persistent benefit for eluxadoline.
- All three clinical trials were placebo-controlled, with high observed placebo response rates. 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 compared with the eluxadoline arm. This potentially overestimates the QALY gains for eluxadoline.

- 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.
- 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.

CDR conducted a reanalysis that assumed patients on eluxadoline and patients on NPT would have similar persistence, assumed no relative benefit after stopping treatment, assumed no ongoing costs for scoping beyond the first year, and excluding study 2001. The result of the CDR reanalysis was an incremental cost-utility ratio of $105,829 per QALY for eluxadoline compared with NPT. A price reduction of 50% to 60% would be required to achieve an incremental cost-utility ratio of $50,000 per QALY.

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

July 18, 2018, Meeting

Regrets

None

Conflicts of Interest

None