CDEC FINAL RECOMMENDATION

LINACLOTIDE
(Constella — Actavis Specialty Pharmaceuticals Co.)
Indication: Irritable Bowel Syndrome With Constipation

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that linaclotide not be listed for the treatment of adults with irritable bowel syndrome with constipation (IBS-C).

Reasons for the Recommendation:

1. Two double-blind, randomized controlled trials (RCTs) (study MD-31 [N = 803] and study 302 [N = 805]) demonstrated that a statistically significantly greater proportion of linaclotide-treated patients achieved responses for abdominal pain, complete spontaneous bowel movements (CSBM), and two combined end points of abdominal pain and CSBM, but the response rates were low and absolute differences between linaclotide and placebo were small.
2. The validity of the studies is limited by the following: the 12- to 26-week duration of the studies was short, given that IBS-C is a condition that may require lifelong treatment; there was a high proportion of patients who withdrew from the trials early (i.e., 23% to 27% in the linaclotide groups and 16% to 24% in the placebo groups); the trials used strict enrolment criteria that screened out a large number of patients (i.e., the proportion of screened patients who were eventually randomized was limited to 33% and 34% in studies MD-31 and 302, respectively); and the trial populations were composed of patients with low rates of background therapies for IBS-C at baseline, which limits the generalizability of the study findings to IBS-C patients likely to be encountered in routine clinical practice. Overall, given the small magnitude of improvements and the limitations of the available evidence, CDEC considered the clinical benefit of treatment with linaclotide in the general population of IBS-C to be uncertain.

Background:
Linaclotide is an orally administered guanylate cyclase-C agonist indicated for the treatment of IBS-C in adults. Linaclotide is available as 145 mcg and 290 mcg capsules and the recommended dosage for the treatment of IBS-C is 290 mcg taken orally once daily on an empty stomach, at least 30 minutes prior to the first meal of the day. Linaclotide is also indicated for the treatment of chronic idiopathic constipation in adults at a dose of 145 mcg per day.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals with IBS-C.

Patient Input Information
The following is a summary of key information provided by one patient group, consisting of patients and caregivers, which responded to the CDR call for patient input:

- Patients with IBS-C experience increased pressure on the bowels, bloating, abdominal cramping, back pain, general malaise, poor appetite, feelings of rectal pressure or fullness, and a sensation of incomplete evacuation. In addition, hemorrhoids, anal fissures, diverticular disease, rectal bleeding, and rectal prolapse are often experienced as complications from intense straining while trying to pass stool.
- The symptoms of IBS-C can negatively affect a person's ability to work, participate in everyday activities, and care for family members. This can to lead to increased isolation, depression, a sense of demoralization, and social stigma.
- Currently available therapy includes diet and exercise, physiotherapy, bulk-forming agents, stool softeners, enemas, lubricants, stimulants, and hyperosmotics. Patients reported that many of these therapies were limited by side effects or a loss of effectiveness over time, that some were never effective or actually worsened their symptoms, and that many patients spent considerable amounts of money purchasing products that were, in the end, all inadequate to varying degrees.

Clinical Trials
The CDR systematic review included two multi-centre, manufacturer-sponsored, phase 3, double-blind RCTs (study MD-31 [N = 803] and study 302 [N = 805]). Both studies randomized patients (1:1) to either linaclotide or placebo. The included studies enrolled patients who exhibited abdominal pain as well as classic bowel symptoms of IBS-C, including a low number (fewer than 3) spontaneous bowel movements (SBMs) per week, and issues with straining, consistency, and sensation of incomplete evacuation. Patients with gastrointestinal comorbidities were excluded.

MD-31 had a 12-week treatment period where linaclotide was compared with placebo. This was followed by a four-week randomized withdrawal phase. In this phase, patients in the linaclotide group were re-randomized to either linaclotide or placebo, and patients previously on placebo were assigned to linaclotide. Study 302 had a 26-week treatment period in which linaclotide was compared with placebo.

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

- Abdominal pain and constipation (APC) 3+1 responders — defined as patients who were APC 3+1 responders for at least nine of the 12 weeks of the treatment period (APC 3+1 9/12). For each week in the treatment period, a weekly APC 3+1 responder was a patient who had at least three CSBMs for the week and an increase of at least one CSBM from baseline for that week, and also had a decrease of at least 30% in their mean abdominal pain score for that week. These were also evaluated as individual end points: CSBM 3+1 9/12 responders (patients who had at least three CSBMs and an improvement of ≥ 1 CSBM over

baseline (CSBM 3+1 response) per week, for at least nine of 12 weeks) and abdominal pain responders, 9/12 weeks.
- APC +1 6/12 responders — defined as patients who had a decrease in their abdominal pain score of at least 30% and an increase during a given week of at least one CSBM from baseline, for at least six of the 12 weeks of the treatment period.
- SBM — defined as a bowel movement that occurred in the absence of laxative, enema, or suppository use. The minimal clinically important difference (MCID) for mean weekly SBM is considered to be 1.9.
- CSBM — defined as an SBM that was associated with a sense of complete evacuation. The MCID is estimated to be between 1.3 and 1.5.
- Severity of straining — assessed by the patient using a 5-point scale (range from 1 [not at all] to 5 [an extreme amount]). The MCID for severity of straining, reported weekly, is considered to be −0.8.
- Abdominal cramping — measured using an 11-point scale to evaluate the severity of abdominal cramping over the previous 24 hours (ranges from 0 [no cramping] to 10 [very severe cramping]).
- Abdominal pain — measured using an 11-point scale to evaluate the severity of abdominal cramping over the previous 24 hours (ranges from 0 [no pain] to 10 [very severe pain]).
- IBS-QOL — a 34-item questionnaire that assesses domains of symptoms, functional status, perceived quality of life, and social disability.

Both of the included studies had four primary outcomes: APC 3+1 responders (9/12 weeks), CSBM 3+1 responders (9/12 weeks), abdominal pain responders (9/12 weeks), and APC +1 responders (6/12 weeks).

Efficacy

- There was a statistically significantly greater proportion of CSBM 3+1 9/12 responders in the linaclotide groups (18% to 20%) compared with the placebo groups (5% to 6%) of both studies. The odds ratios were:
  - Study MD-31: 3.7 (95% confidence interval [CI], 2.3 to 5.9); $P < 0.0001$
  - Study 302: 4.2 (95% CI, 2.5 to 7.0); $P < 0.0001$.
- The weekly mean CSBM increased in both the linaclotide (2.24 to 2.27) and placebo groups (0.70 to 0.71) of both studies. The least squares mean difference between groups was statistically significant in both studies:
  - MD-31: 1.57 (95% CI, 1.24 to 1.90); $P < 0.0001$
  - Study 302: 1.54 (95% CI, 1.23 to 1.85); $P < 0.0001$.
- There was a statistically significant improvement in weekly SBM rates in the linaclotide groups compared with the placebo groups. The least squares mean differences between groups were:
  - Study MD-31: 2.77 (95% CI, 2.32 to 3.22)
  - Study 302: 2.70 (95% CI, 2.26 to 3.15).
- A statistically significantly greater proportion of linaclotide-treated patients were abdominal pain responders compared with placebo-treated patients in both studies MD-31 (34% versus 27%) and 302 (39% versus 20%). The odds ratios for achieving an abdominal pain response were:
  - Study MD-31: 1.4 (95% CI, 1.0 to 1.9); $P = 0.0262$
  - Study 302: 2.6 (95% CI, 1.9 to 3.6); $P < 0.0001$.

- A statistically significantly greater proportion of linaclotide-treated patients were APC 3 + 1 and APC + 1 responders compared with placebo-treated patients in both studies. The odds ratios, in MD-31 and study 302, respectively, were:
  - APC 3 + 1 responder: 2.60 (95% CI, 1.51 to 4.47) and 4.65 (95% CI, 2.44 to 8.84)
  - APC + 1 responder: 1.93 (95% CI, 1.40 to 2.66) and 3.16 (95% CI, 2.22 to 4.49)
- Abdominal pain, abdominal discomfort, bloating, stool consistency, and straining were all statistically significantly improved in the linaclotide treatment groups compared with the placebo treatment groups. The least squares mean differences between linaclotide and placebo were (studies MD-31 and 302, respectively):
  - Abdominal pain: −0.74 (95% CI, −0.98 to −0.50) and −0.78 (95% CI, −1.02 to −0.55)
  - Abdominal discomfort: −0.74 (95% CI, −0.99 to −0.49) and −0.84 (95% CI, −1.07 to −0.60)
  - Bloating: −0.84 (95% CI, −1.10 to −0.59) and −0.88 (95% CI, −1.12 to −0.64)
  - Stool consistency: 1.41 (95% CI, 1.25 to 1.57) and 1.31 (95% CI, 1.15 to 1.47).
- Quality of life was evaluated using the IBS-QOL scale as an exploratory end point [redacted]

Harms (Safety and Tolerability)

- The proportions of patients who experienced at least one serious adverse event were:
  - Study MD-31: 1% in both the linaclotide and placebo groups
  - Study 302: 1% with linaclotide and 2% with placebo.
- Withdrawals due to adverse events were more commonly reported in the linaclotide groups compared with the placebo groups, with diarrhea being the most common adverse event leading to discontinuation. The proportions of patients who withdrew as a result of adverse events were:
  - Study MD-31: 8% with linaclotide and 3% with placebo
  - Study 302: 10% with linaclotide and 3% with placebo.
- The most commonly reported adverse event in linaclotide-treated patients was diarrhea, occurring in 20% of patients in the linaclotide groups of both studies compared with 3% to 4% of patients in the placebo groups. The proportions of patients who experienced at least one adverse event were:
  - Study MD-31: 56% with linaclotide and 53% with placebo
  - Study 302: 65% with linaclotide and 57% with placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing the cost-effectiveness of linaclotide against no treatment (placebo) in adult patients with IBS-C. The decision tree model was based on the following final states: failure (discontinuation); failure (no response); and improvement (response). Responders were defined as those with an APC 3+1 6/12 response and were assumed to continue treatment for the duration of the one-year time horizon. Patients who moved into the failure category were assumed to receive treatment for 30 days. Utility values were assigned for the failure and improvement states, and were assumed to vary by treatment at baseline — differences were assumed to continue after treatment was curtailed. Costs were assigned to the failure and improvement states with minimal resource use assigned to the improvement state. The analysis was undertaken from a public-payer perspective.

CDR identified a number of limitations with the manufacturer's economic evaluation:

- The manufacturer assumed that patients on linaclotide who failed to achieve a response would stop therapy after 30 days. The outcome used to define response relates to 12 weeks of treatment. Thus, an assumption of 12 weeks of treatment for patients who are non-responders may be more appropriate.
- The model is defined by two states: improvement and failure. The manufacturer assumed differential utility values within these states for placebo and linaclotide, which is inappropriate. If health status is assumed to vary within health states, then more refined definitions of states should be used. Further, as patients who fail on therapy are assumed to discontinue after 30 days, the utility values associated with linaclotide should not apply.
- Based on findings from the clinical trials, no differences in resource use between linaclotide and placebo patients were noted. The manufacturer assumed negligible resource use for patients who were responders, which benefits linaclotide and for which little justification is available.
- The manufacturer compared linaclotide with placebo in its analysis; no other comparators were considered. Although linaclotide is the only treatment specifically indicated for IBS-C, other therapies indicated for a broader diagnosis could have been considered (e.g., fibre or laxatives). The cost-effectiveness of linaclotide compared with other treatment options, which could provide symptom relief, could not be addressed.

The manufacturer reported that the incremental cost per quality-adjusted life-year (QALY) for linaclotide compared with no treatment was $17,758 (an incremental cost of $604 and incremental QALYs of 0.0344). Based on a revised analysis accounting for the above limitations, CDR found that the incremental cost per QALY gained increased to $102,376 for linaclotide compared with no treatment. In this scenario, a 50% price reduction would be required for the incremental cost per QALY to fall to $49,000.

Based on the manufacturer's submitted price ($5.30 per 290 mcg capsule), the cost of treatment with linaclotide is $5.30 per day and $1,935 per year (at the recommended dose).

Other Discussion Points:

CDEC noted the following:

- CDEC noted that patient input identified quality of life as a key consideration in IBS-C. The included studies were not designed to assess quality of life other than as an exploratory outcome, and statistical differences should be interpreted with caution as the comparisons were not included in the trials' hierarchical strategy for multiplicity. Quality of life improvements were seen in both treatment and placebo groups over the course of the trials; however, the observed differences between the groups did not achieve the clinically important differences in the Irritable Bowel Syndrome Quality of Life measure (IBS-QOL) that have been established in similar populations.
- Studies MD-31 and 302 enrolled a highly selected patient population with low background usage of concurrent therapies. This is an important limitation of the studies, as a large proportion of IBS-C patients in Canada would likely be using concurrent therapies. In addition, CDEC considered patients whose IBS-C was inadequately controlled despite the use of optimized background therapies to be a relevant subpopulation for this review; however, there was insufficient evidence for the committee to determine if treatment with linaclotide improves IBS-C symptoms in this patient population.
- The high proportion of patients in the linaclotide groups who experienced diarrhea may have compromised blinding for some patients and investigators.

- There was a lack of clarity regarding how the statistical analysis was performed for the primary efficacy end points.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- IBS-C is a chronic disorder and the long-term safety and efficacy of linaclotide in the treatment of IBS-C requires further evaluation.
- There are no direct or indirect comparisons of linaclotide against other active treatments used in the management of patients with IBS-C.
- There are limited data regarding the efficacy of linaclotide when used in combination with other active treatments for IBS-C.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

Regrets:

June 17, 2015: One CDEC member was unable to attend the meeting.
September 16, 2015: None

Conflicts of Interest:

None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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