CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

TELOTRISTAT ETHYL (XERMELO — IPSEN BIOPHARMACEUTICALS CANADA INC)
Indication: For the treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients inadequately controlled by SSA therapy alone.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that telotristat ethyl not be reimbursed for the treatment of refractory carcinoid syndrome diarrhea, in combination SSA therapy, in patients inadequately controlled by SSA therapy alone.

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that telotristat ethyl not be reimbursed for the treatment of refractory carcinoid syndrome diarrhea, in combination SSA therapy, in patients inadequately controlled by SSA therapy alone.

Reasons for the Recommendation

1. In one double-blind, placebo-controlled RCT (TELESTAR; N=135), telotristat was associated with a statistically significant greater reduction in the number of daily bowel movements compared to placebo over 12 weeks, but the magnitude of this difference between telotristat and placebo (0.8 fewer bowel movements in telotristat-treated patients; 97.5% CI: -1.256, -0.280; p<0.001) was of uncertain clinical relevance. Telotristat failed to improve symptoms of importance to patients that are associated with diarrhea such as urgency and did not improve a variety of health-related quality of life subscales associated with this condition (fatigue, body image, pain, impact on finances, and social/cognitive functioning). Moreover, telotristat did not improve other symptoms associated with carcinoid syndrome, namely abdominal pain and flushing.
2. Patients in TELESTAR received concomitant SSA therapy (octreotide and lanreotide). Some patients had their SSA therapy optimized with escalated doses while others continued to receive standard doses. It is unclear what effects telotristat would have in patients with carcinoid syndrome diarrhea that is inadequately controlled by optimized SSA therapy.

Discussion Points

- The committee noted TELESTAR did not compare telotristat to other treatments that may be used in clinical practice, including loperamide, diphenoxylate, opioids, rescue subcutaneous SSAs, or increased dosage of sustained release intramuscular SSA. Because of the lack of randomized clinical trial-based evidence on the use of non-SSA treatments in patients with carcinoid syndrome, the effects of telotristat compared to non-SSA treatments in this population are unclear.
- Only 40.0% of patients in the control arm and 42.2% of patients in the telotristat arm of TELESTAR received higher than standard doses during the trial (standard doses: octreotide LAR 30mg every 4 weeks or lanreotide 120mg every 4 weeks). Dose escalation of SSA therapy with octreotide LAR up to 60 mg every 2 to 4 weeks or lanreotide up to 180 mg every 3 weeks is identified as an appropriate approach for symptom control and is supported by Canadian expert opinion. The administration of pancreatic enzymes, as necessary to avoid progressive steatorrhea due to pancreatic insufficiency secondary to SSA dose escalation, is also supported by expert opinion.
- The committee noted that 32 patients were excluded from TELESTAR if they had, among other criteria, received any therapy that was directed at the tumor itself, had a life expectancy less than 12 months, had diarrhea attributable to other conditions, or displayed frequent (more than 12 bowel movements a day) watery diarrhea. The committee concluded that TELESTAR did not reflect patients presenting with severe symptoms in clinical practice, who would be the most likely to require, and benefit from, adjunctive antidiarrheal therapy.
- The manufacturer reported a responder analysis which examined the percentage of patients who had at least a 30% reduction from baseline in the number of bowel movements for at least 50% of the 12-week-long double-blind treatment period in TELESTAR. The committee noted that although the proportion of responders in the telotristat group was higher than in the placebo group (44% versus 20%) in this analysis, this was an exploratory outcome that was not adjusted for multiple comparisons, thus increasing the risk of a Type I error. Moreover, the clinical relevance of a 30% reduction in the number of bowel movements is unclear.

Background

Telotristat has a Health Canada indication for treatment of refractory carcinoid syndrome diarrhea in combination with somatostatin analogue therapy, in patients inadequately controlled by somatostatin analogue therapy alone. Telotristat is a tryptophan hydroxylase inhibitor. It is available as orally administered tablets and the Health Canada approved dose is 250mg three times daily.

Summary of Evidence Considered by CDEC Considerations

The committee considered the following information prepared by the Common Drug Review: a systematic review of one double-blind randomized controlled trial of telotristat and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with carcinoid syndrome diarrhea, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group (Carcinoid Neuroendocrine Tumour Society of Canada) provided input for this submission. Patient perspectives were obtained from a large global net survey conducted in 2015 (N=1928) and a smaller online survey conducted in 2018 (N=11). The following is a summary of key input from the perspective of this patient group:

- Patients described diarrhea as having the largest impact on health-related quality of life, followed by fatigue/weakness, flushing/rash, abdominal pain, sweating/headaches, anxiety and breathlessness. Living with the condition had the largest impact on finances, ability to work, energy levels, and travel, and well as having an emotional impact, an impact on social life and relationships.
- Regarding unmet needs, patient responses were generally restricted to surgical interventions, and the issues were generally related to the invasiveness of the procedures, as well as long recovery times as well as adverse effects and complications. Patients who had experience with lanreotide did note that the requirement for injections every three weeks was inconvenient.
- Ten respondents to the survey had experience with telotristat, and all noted diarrhea control as the most important outcome associated with the drug. They also noted that the expectation was that this improvement in diarrhea control would also improve quality of life, as it would improve social function, energy, and self-esteem. Nine respondents found the therapy to be beneficial, one discontinued telotristat therapy due to adverse effects and all others found it tolerable with adverse effects that had little or no impact on their quality of life.

Clinical Trials

The systematic review included one double-blind randomized placebo-controlled trial (TELESTAR) of patients with carcinoid syndrome associated diarrhea, on a stable dose of somatostatin analogues. Patients also had to have a minimum of 4 bowel movements daily to be included in the trial.

TELESTAR compared two doses of telotristat (250mg or 500mg three times daily) to placebo in 135 patients. Only the Health Canada approved 250mg dose was considered in this systematic review. The initial double-blind treatment period was 12 weeks and patients were randomized in a 1:1:1 manner between groups. The primary outcome was the mean change from baseline in number of daily bowel movements, compiled over the 12-week double blind treatment period. There were 7% of patients in the telotristat group who withdrew versus 16% of those in the placebo group.

Key limitations of the trials included a difference of 0.8 bowel movements per day between comparison groups at baseline. The fact that no health-related quality of life outcomes were adjusted for multiple statistical comparisons, a higher proportion of withdrawals were experienced in the placebo group than with telotristat, the lack of an intention to treat analysis of urinary 5-hydroxyindoleacetic acid levels and health-related quality of life outcomes, and the relatively short follow up and small sample size, all limit conclusions that can be drawn about potential for long term harms with telotristat.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following: change from baseline in daily bowel movements, symptoms (abdominal pain, flushing), health-related quality of life, stool consistency and urgency to defecate. The primary outcome in the trial was the mean change from baseline in number of daily bowel movements, compiled over the 12-week double blind treatment period.

- Health-related quality of life was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30, and the Gastrointestinal Symptoms of Neuroendocrine Tumours (GI.NET) instruments. The QLQ-C30 is a 30-item patient-reported questionnaire that includes five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/QoL scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The scores for each were transformed to arrive at a standardized score of between zero and 100, and the minimum clinically important difference (MCID) was 10. The 21-item GI.NET scale encompasses three endocrine symptoms, five gastrointestinal symptoms, and three items that assess treatment-related side effects. There are also two single items for muscle and/or bone pain and for concern about weight loss. A linear transformation was also performed to arrive at a score that ranged from zero to 100. No MCID was identified for the GI.NET scale.
- Abdominal pain was assessed on an 11-point scale ranging from zero ('no pain') to 10 ('worst pain ever experienced').
- Stool quality was assessed using the Bristol Stool Form Survey, an ordinal scale that ranges from type 1 (hardest) to type 7 (softest). Types 1 and 2 were considered to be abnormally hard and indicative of constipation, while types 6 and 7 were considered abnormally loose/liquid stools indicative of diarrhea.
- The manufacturer also developed a responder analysis for bowel movement frequency as an exploratory outcome. A responder was defined as a patient who experienced at least a 30% reduction from baseline in daily bowel movements at least 50% of the double blind 12-week treatment period.

Efficacy

In TELESTAR, the Hodges Lehman estimate of treatment difference in reduction in the number of daily bowel movements from baseline compiled over the 12-week treatment period with telotristat versus placebo was 0.812 (97.5% CI: -1.256, -0.280; p<0.001). The manufacturer also reported a responder analysis, an exploratory outcome, which examined the percentage of patients who had at least a 30% reduction from baseline in bowel movements for at least 50% of the 12-week double blind treatment period. There were a higher percentage of responders in the telotristat group versus placebo (44% versus 20%).

There were no statistically significant differences between telotristat and placebo for daily flushing episodes or episodes of abdominal pain over the 12-week double-blind treatment period. These were both secondary outcomes in this study and thus statistical analysis was adjusted for multiple comparisons. The Hodges Lehman estimate of treatment difference between groups was 0.036 counts/day [97.5% confidence limit: -0.230, 0.330] p=0.39 for flushing episodes and -0.168 [97.5% confidence limit: -0.541, 0.224] for abdominal pain scores.

Quality of bowel movements was assessed by stool consistency using the Bristol Scale. Across the 12-week double-blind treatment period in TELESTAR, stool consistency scores decreased in the telotristat group (mean [SD] change from baseline of -0.265 [0.4712]) and in the placebo group (-0.216 [0.4791]), for an HL estimate of difference between groups of -0.087 [95% CI: -0.268 to 0.110], p=0.57. This was an exploratory analysis and no MCID could be found so the clinical significance is unclear.

Health-related quality of life was assessed using the EORTC QLQ-C30 and GI.NET as exploratory outcomes, both averaged over weeks 6 and 12 and reported at week 6 and at week 12 separately. There were no statistically significant differences between telotristat and placebo for a majority of subscales. Since none of the HRQoL scores were adjusted for multiple comparisons, no conclusions should be drawn regarding the few subscales reported as statistically significant.

There was a statistically significant reduction in urinary 5-HIAA in the telotristat group compared to placebo at week 12 (Hodges Lehman Estimator of treatment difference of -30.100 [97.5% Confidence interval: -55.800, -9.200]; p<0.001). This was the first secondary outcome in the statistical hierarchy and therefore was adjusted for multiple comparisons. This reduction from baseline was considered to be clinically significant by the clinical expert consulted on this review.

Harms (Safety)

- There was one death in the telotristat group versus three deaths with placebo. Serious adverse events occurred in 16% of patients in each group.
- Adverse events occurred in 82% of telotristat patients versus 87% with placebo after 12 weeks. The most common adverse events were nausea (13% of telotristat versus 11% placebo), and abdominal pain (11% versus 18%).
- Withdrawals due to adverse event occurred in 4% of telotristat versus 16% of placebo patients.
- Notable harms include depression, which occurred in 4% of patients in the telotristat group and 7% of patients in the placebo group, and constipation (zero in the telotristat group and 4% with placebo). Depression is noted under Warnings in the Product Monograph, as there was an indication of increased risk of depression at the higher telotristat 500mg dose (not reported in this review), however the lower approved dose does not appear to be linked with depression in this 12-week study. Elevated liver enzymes only occurred in telotristat patients (ALT increased: 2% versus zero, and GGT increased: 9% versus zero), and no patients had increased ALP.

Cost and Cost-Effectiveness

Telotristat is available as a 250 mg oral tablet, at a submitted list price of $84.82 per tablet. The recommended daily dose is 250 mg three times daily, resulting in an annual cost of $92,199 per patient.

The manufacturer submitted a cost-utility analysis of telotristat in combination with SSA therapy compared to SSA monotherapy alone over a 30-year time horizon, from the perspective of the Canadian public health care payer. Patients received either the telotristat and SSA combination therapy or SSA monotherapy at the start of the model. Patients showing durable response to treatment over the first 12 weeks, defined as ≥30% reduction in bowel movement (BM) frequency for ≥50% of the 12-week period, were assumed to continue treatment with telotristat + SSA until discontinuation or death. Those who did not show durable response were assumed to switch to SSA monotherapy. The manufacturer incorporated efficacy parameters based on the TELESTAR trial, and mortality parameters based on the CLARINET trial. Health state utilities were based on a published valuation study conducted in the general UK population.

The manufacturer reported that telotristat + SSA therapy was associated with an incremental cost-utility ratio (ICUR) of $836,293 per quality-adjusted life year (QALY). The manufacturer also undertook several scenario analyses, including the consideration of subsequent therapy post treatment failure, assuming a 100% response rate, which had the greatest impact with an ICUR between $5.7 million and $13.1 million per QALY, depending on the cost of subsequent therapy.

CDR identified the following key limitations:

- Health states in the economic model were defined in terms of remaining on or discontinuing treatment, rather than in terms of the health states experienced by the patient. Using this approach, it was not possible to establish what was causing differences in utility values between treatments. Due to the model structure, it was not feasible to address this limitation.
- Utility values used by the manufacturer were not based on the TELESTAR trial but sourced from a published study which found a larger difference (i.e., 0.171) in utility values between treatment responders and non-responders compared to the observed utility difference in the TELESTAR trial (i.e., 0.073), favoring telotristat. CDR addressed this limitation by using utility data based on the TELESTAR trial.
- Long-term validity of model parameters and assumptions, particularly those related to efficacy, survival, and subsequent therapy, are uncertain as they are based on short-term trial evidence which was extrapolated to a 30-year time horizon.

In the CDR base case using the utility values derived from the TELESTAR trial, the ICUR for telotristat + SSA was $1.96 million per QALY compared with SSA monotherapy. The estimate is associated with notable uncertainty due to limitations pertaining to the model structure and the availability of clinical information. Based on the CDR base case, a price reduction of at least 95% would be required for telotristat to achieve an ICUR less than $100,000 per QALY, and more than 97.5% for ICUR less than $50,000 per QALY.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

February 20, 2019 Meeting

Regrets

One member did not attend.

Conflicts of Interest

None

June 19, 2019 Meeting

Regrets

None

Conflicts of Interest

None