CDEC FINAL RECOMMENDATION

LOMITAPIDE
(Juxtapid — Aegerion Pharmaceuticals Inc.)
Indication: Homozygous Familial Hypercholesterolemia

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that lomitapide not be listed to reduce low-density lipoprotein cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolemia (HoFH).

Reasons for the Recommendation:

1. The efficacy data are limited to surrogate end points that were evaluated in a single, uncontrolled, open-label pivotal study (N = 29). Although treatment with lomitapide was associated with a statistically significant percentage decrease from baseline in LDL-C (–40.1%; 95% confidence interval [CI], –51.9% to –28.2%), there was no evidence for CDEC to evaluate the cardiovascular (CV) benefit of lomitapide.
2. Lomitapide is associated with significant hepatic adverse events. A majority of the patients (18 of 23; 78.3%) in an open-label phase 3 trial developed hepatic steatosis (i.e., hepatic fat > 5.6%, as measured by nuclear magnetic resonance spectroscopy), the long-term consequences of which are unknown. HoFH is a chronic condition and lomitapide is intended for long-term use in these patients; therefore, the clinical relevance of the observed increase in hepatic fat, including the risk of progression to steatohepatitis and cirrhosis, requires further evaluation.

Background:
Lomitapide inhibits the transfer of triglyceride onto apolipoprotein (apo) B-100 in the liver, preventing the formation of very low-density lipoproteins (VLDL), thereby reducing circulating levels of LDL-C.

Lomitapide has a Health Canada indication as an adjunct treatment to a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis, to reduce LDL-C in adult patients with HoFH. Lomitapide is initiated at a dose of 5 mg orally once daily and increased to 10 mg daily after two weeks. The dose is subsequently increased at four-week intervals to 20 mg, then 40 mg, up to a maximum of 60 mg daily according to safety standards and tolerability. Lomitapide is available as 5 mg, 10 mg, and 20 mg capsules.

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

Patient Input Information
The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- Patients with familial hypercholesterolemia often experience CV complications such as atherosclerosis, stroke, atrial fibrillation, chest pain, and heart attack, requiring frequent hospital-based medical or surgical interventions.
- Psychological consequences include the ever-present anxiety of living with a "ticking bomb" as a consequence of witnessing familial hypercholesterolemia-related complications and deaths in affected family members and knowing their own excess CV risk is insufficiently mitigated with current treatments.
- A majority of patients reported receiving apheresis treatments every one to three weeks. These were described as burdensome, disrupting school, work, and social activities. Some patients reported being so tired following apheresis treatments that they had to decrease their work or school commitments from full- to part-time. Patients expressed a desire for a drug treatment that would enable a reduction in the frequency of apheresis treatment sessions.

Clinical Trials
The CDR systematic review included one phase 3 (UP1002/AEGR-733-005) multi-national, open-label, single-group, uncontrolled study that included 29 patients with a diagnosis of HoFH. The study was divided into two phases: a 26-week efficacy phase, during which the maximally tolerated dose of the study drug was established through a forced dose-titration protocol (5 mg to 60 mg/day); and a 52-week safety phase, during which the maximally tolerated dose established from the efficacy phase was continued at the same dose until week 78. All patients received lomitapide in combination with background lipid-lowering therapy. Changes in concomitant lipid-lowering treatments, including apheresis, were not permitted during the 26-week efficacy phase, but were permitted during the subsequent safety phase.

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

- Per cent change from baseline in LDL-C and other lipid parameters at 26 weeks.
- Frequency of apheresis treatments.
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

The primary efficacy outcome in UP1002/AEGR-733-005 was the per cent change from baseline in LDL-C after 26 weeks.

Efficacy

- Treatment with lomitapide was associated with a statistically significant percentage decrease from baseline in LDL-C (–40.1%; 95% CI, –51.9% to –28.2%). Statistically

significant incremental reductions in LDL-C were observed at each visit and reached a nadir of –45.0% at week 18 and then began to drift slightly upward to –40.7% at week 22.
- After 26 weeks, a statistically significant reduction in non–high-density lipoprotein cholesterol (HDL-C) was observed from baseline (–40.0%; 95% CI, –51.3% to –28.8%). As with LDL-C, statistically significant incremental reductions in non-HDL-C were noted at each visit (except week 2) and reached a nadir of –52.7% at week 18, then began to drift slightly upward to –46.7% at week 22.
- Lomitapide was associated with statistically significant reductions in the following lipid parameters (per cent change [standard deviation]): total cholesterol (–36.4% [28.2]; $P < 0.001$); apo B (–39.4% [30.0]; $P < 0.001$); triglycerides (–29.0% [55.7]; $P = 0.009$); VLDL-C (–28.6% [57.5]; $P = 0.012$); and apo A1 (–6.5% [16.1]; $P = 0.038$). Changes from baseline in HDL-C were not statistically significant (–6.9% [19.8]; $P = 0.072$).
- The frequency of apheresis treatments was not modifiable during the 26-week efficacy phase of the study. Of the 13 patients who were also receiving apheresis at the beginning of the safety phase, 3 (23.1%) were able to completely stop apheresis treatment and another 3 (23.1%) were able to lengthen the interval between apheresis treatments through week 78.

Harms (Safety and Tolerability)
- The overall frequency of adverse events was comparable during the 26-week efficacy and 52-week safety phases (93.1% versus 91.3%). Diarrhea, nausea, and vomiting were the most commonly occurring adverse events for both phases, though the frequencies were higher during the efficacy phase (79.3%, 62.1%, and 27.6%) than the safety phase (34.8%, 30.4%, and 21.7%).
- Serious adverse events occurred in 10.3% of patients during the efficacy phase, but in 0% of patients during the safety phase.
- Withdrawals due to adverse events were reported for 13.8% of patients during the efficacy phase and for 0% of patients during the safety phase.

Cost and Cost-Effectiveness
The manufacturer submitted a cost-consequence analysis presenting the costs and clinical outcomes associated with lomitapide as an adjunct to standard of care, defined as lipid-lowering therapy with or without plasma exchange, compared with standard of care alone in adult patients with HoFH. The perspective was that of a Canadian public health payer during a five-year time horizon. LDL-C was used as a surrogate marker to predict a potential reduction in the risk of CV event with lomitapide plus standard of care compared with standard of care alone. This assumption was based on retrospective studies with statins (not involving lomitapide) that showed a modest reduction in LDL-C to have resulted in improvement in morbidity and mortality. Total costs included drug cost, cost of plasma exchange (26 sessions per year), as well as costs associated with major adverse cardiac events (myocardial infarction, coronary procedures, other vascular procedures, cerebrovascular events, and cardiovascular death). The manufacturer assumed a 21% treatment discontinuation rate in the first year, and no discontinuation in subsequent years. Patients who discontinued incurred half a year cost of lomitapide treatment and half a year treatment benefit in the year of discontinuation. Patients treated with lomitapide were assumed to be 88% compliant in the first year and 100% compliant in subsequent years. The manufacturer estimated that, over five years, lomitapide plus standard of care compared with standard of care alone may result in reductions in CV events ranging from 45% to 57%.

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

- The comparative effectiveness of lomitapide plus standard of care versus standard of care alone has not been determined from the currently available evidence; and the validity of change in LDL-C as a surrogate for outcomes such as CV events or CV death in HoFH patients is not well established.
- The manufacturer assumed that patients receiving lomitapide may discontinue or reduce the frequency of plasma apheresis sessions, but this might not be the case due to the severity of the condition.
- The manufacturer did not include the costs incurred from periodic monitoring of liver function tests and per cent hepatic fat from baseline, or costs related to the management of these adverse events, which were more frequent with lomitapide, and therefore would have been relevant to include.
- The baseline patient data used in the model were based on a study with very small numbers of patients and data that were not specific to the Canadian population.

CDR conducted a reanalysis that assumed HoFH patients treated with lomitapide will continue bi-weekly sessions of plasma exchanges. The CDR reanalysis suggests the annual cost per HoFH patient treated with lomitapide would be $310,132 compared with the annual cost with standard of care of $14,339 per HoFH patient.

Exploratory cost-effectiveness analyses by CDR based on suggested benefits by the manufacturer estimated incremental cost-effectiveness ratios (ICERs) varying from $13.5 million per coronary procedure avoided to $512 million per cerebrovascular event avoided. However, given that the relationship between LDL change and the suggested benefits is uncertain, these results should be interpreted with caution. The comparative effectiveness, impact on quality of life, and consequently the cost-effectiveness of lomitapide plus standard of care compared with standard of care alone remain unknown.

At the submitted price of $1,040 per day (patient cap specifies that the maximum cost per patient will not exceed $1,040 per day, irrespective of the dose prescribed and strengths dispensed), the annual cost of lomitapide is $379,600.

Other Discussion Points:

CDEC noted the following:

- Although permitted in the safety phase, the protocol of the pivotal study did not permit changes in concomitant lipid-lowering treatments during the 26-week efficacy phase. This design precluded a robust evaluation of the potential for lomitapide to reduce the need for apheresis treatment.
- CDEC noted that the listing criteria proposed by the manufacturer do not allow for the accurate identification of patients with HoFH. A large number of mutations have been identified in the genes involved in HoFH, including approximately 900 for the LDL-receptor alone. A diagnosis of homozygous HoFH is unlikely to be made based solely on the presence or absence of mutations in genes for the LDL-receptor (LDL-R), apo B, proprotein convertase subtilisin/kexin type 9 (PCSK9), or the autosomal recessive hypercholesterolemia (ARH) LDL-R adapter protein. The diagnosis and the decision to initiate management of HoFH require clear clinical parameters, including accepted LDL-C thresholds. CDEC was unable to identify a clear LDL-C threshold for initiating treatment with lomitapide.

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

- The effect of lomitapide on CV morbidity and mortality. This effect has not been determined and the long-term safety profile requires further evaluation. In accordance with post-market requirements of the US Food and Drug Administration and the European Medicines Agency, the manufacturer is conducting a long-term observational cohort study using a global registry to evaluate the long-term safety and effectiveness of lomitapide in HoFH. The estimated enrolment in the registry study is 300 patients with a target follow-up of 10 years.
- The impact of lomitapide on the quality of life of patients has not been evaluated.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

March 18, 2015 Meeting

Regrets:

One CDEC member was unable to attend the meeting.

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 not requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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