pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Lenvatinib (Lenvima) **Submitted Reimbursement Request:** For the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC)	
Submitted By: Eisai Limited	**Manufactured By:** Eisai Limited
NOC Date: December 19, 2018	**Submission Date:** February 8, 2019
Initial Recommendation: July 05, 2019	**Final Recommendation:** July 24, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Lenvatinib costs $8.1429 per mg. At the recommended dose of: • 8 mg per day (< 60 kg bodyweight), lenvatinib costs $65.1430 per day and $1,824.01 per 28-day course • 12mg per day (> 60 kg bodyweight), lenvatinib costs $97.7145 per day and $2,736.01 per 28-day course

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC recommends reimbursement of lenvatinib (Lenvima) for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC) only if the following condition is met:

- the public drug plan cost of treatment with lenvatinib should not exceed the public drug plan cost of treatment with sorafenib.

Reimbursement should be for patients with Child-Pugh A liver function who have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 and who would otherwise meet the inclusion criteria of the REFLECT trial. Treatment with lenvatinib should continue until confirmed disease progression or unacceptable toxicity.

pERC made this recommendation because it was satisfied that there may be a net clinical benefit of lenvatinib in this setting. This was based on the noninferiority in overall survival for lenvatinib compared with sorafenib, a different toxicity profile compared with sorafenib and no detriment to quality of life (QoL). pERC was also satisfied that lenvatinib aligns with patient values of having a treatment option that offers different and potentially more manageable toxicities compared to sorafenib and provides ease of administration for patients.

Given the likelihood of similarity in efficacy between lenvatinib and sorafenib, pERC concluded that the public drug plan cost of treatment with lenvatinib should not exceed the public drug plan cost of treatment with sorafenib.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Maintain Dominance (i.e., more effective, less costly)** pERC concluded that lenvatinib dominates sorafenib at the list price. pERC noted that the incremental cost-effectiveness ratio for each comparison is most sensitive to the prices of lenvatinib and sorafenib. pERC further noted that the negotiated confidential price of sorafenib is likely lower than the list price used in the submitted economic evaluation. pERC concluded that the public drug plan cost of lenvatinib should not exceed the public drug plan cost of treatment with sorafenib in this setting. **Considerations for switching between sorafenib and lenvatinib should be based on tolerability not progression** pERC noted that there is currently no evidence to help determine which patients may be better suited for lenvatinib or sorafenib treatment. pERC acknowledged that tolerability may be used to select patients (e.g., patients with uncontrolled hypertension may be better suited for sorafenib). For patients who have not progressed radiographically on sorafenib but are sorafenib intolerant, pERC agreed that it would be reasonable to consider switching to lenvatinib. Likewise, it would be reasonable to consider switching to sorafenib for patients who have not progressed radiographically on lenvatinib but are lenvatinib intolerant. pERC noted that these considerations were also supported by input from registered clinicians. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

In 2017, there were approximately 2,500 new cases of hepatocellular carcinoma (HCC) diagnosed in Canada. The treatment approach for, and prognosis of, patients with HCC depends on the extent of the disease, hepatic functional reserve, and performance status. Child-Pugh class (A, B, or C) is the most commonly used metric to assess hepatic reserve. The prognosis for patients with untreated advanced and unresectable HCC is poor, with a median overall survival (OS) of less than one year. Sorafenib is currently approved and reimbursed across Canada for the first-line systemic treatment of patients with Child-Pugh class A advanced HCC. pERC noted that hand-foot syndrome (HFS) is common and a difficult to manage drug-related adverse event with sorafenib. This was reflected by input from patients, registered clinicians, and the Clinical Guidance Panel (CGP). pERC therefore concluded that there is an unmet need in this setting for effective and potentially more tolerable treatment options.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one international, multi-centre, open-label, phase III trial, REFLECT. The trial evaluated the noninferiority (NI) of lenvatinib compared with sorafenib in the first-line treatment of patients with advanced, unresectable HCC with no prior systemic therapy. Noninferiority was demonstrated for OS, the primary end point, in the full analysis set (HR: 0.92, 95% confidence interval [CI], 0.79 to 1.06) based on a noninferiority margin of 1.08, which was defined a priori. The per-protocol analysis demonstrated similar results. Furthermore, the trial demonstrated statistically significant improvement in progression-free survival (PFS) and objective response rate (ORR) in favour of lenvatinib. pERC agreed with the CGP that lenvatinib did not have a detrimental impact on patient's QoL and that the toxicity profile was different from sorafenib. pERC noted that the number of patients experiencing adverse events and serious adverse events were increased with lenvatinib however the toxicities observed with lenvatinib (i.e., hypertension) are more easily managed than those seen with sorafenib (i.e., HFS). Overall, pERC concluded that there may be a net overall clinical benefit with lenvatinib in this patient population based upon demonstrated noninferiority in OS, statistically significant improvements in PFS, ORR, a different yet manageable toxicity profile, and no apparent detriment in QoL compared with sorafenib.

pERC considered the generalizability of the trial results. pERC agreed with the CGP that patients eligible for lenvatinib should align with the inclusion criteria of the REFLECT trial, namely, patients should have an ECOG PS 0-1, have a Child-Pugh A liver function, not have ≥ 50% of liver occupation, clear invasion of the bile duct or portal vein invasion at the main portal branch, and not have a history of or current brain or subdural metastases. pERC further noted that there is no evidence to support the use of lenvatinib to maintain response or as a bridge to transplant. pERC also acknowledged that there is no evidence to sequence the use of lenvatinib and sorafenib. pERC, however, noted that it would be reasonable to switch from sorafenib to lenvatinib and vice-versa before progression if it is deemed appropriate, especially if there is intolerance to the adverse effects of the medications. Lastly, pERC agreed with the CGP in that there is no rationale to suggest that the efficacy of second-line HCC treatments would be influenced by the first-line therapy, since these two drugs have a fairly similar mechanism of action.

Patients noted that they value having access to new treatment options that improve survival, improve QoL, better manage side effects, and control disease. Patients and caregivers also value reduced burden on caregivers. Based on the results of the REFLECT trial, pERC concluded that lenvatinib aligns with patient values of having additional treatment options that provide different side effects than HFS, that may be easier to manage and has no detrimental impact on quality of life.

pERC also deliberated upon the cost-effectiveness of lenvatinib versus sorafenib. pERC noted discussions from the Economic Guidance Panel (EGP) indicating that the submitted model was well designed and robust. pERC noted that cost-effectiveness estimates provided by the submitter and EGP indicated that there was potential incremental benefit associated with lenvatinib. When this was combined with the lower price of lenvatinib, lenvatinib was dominant (more effective and less costly) in all scenarios. Based

on the results of the REFLECT trial, pERC agreed that the efficacy of lenvatinib and sorafenib is likely similar while there appears to be differences in the toxicity profiles. pERC noted that the EGP made modifications to reflect 100% dose intensity and post-progression treatment received by patients. pERC further noted that the EGP's best estimates were based on the current list prices of lenvatinib and sorafenib. While pERC is unaware of the confidential price of sorafenib, pERC anticipates that a lower negotiated price would have an impact on the cost-effectiveness estimates. pERC concluded that the public drug plan cost of treatment with lenvatinib should not exceed the public drug plan cost of treatment with sorafenib.

pERC considered the feasibility of implementing a reimbursement recommendation for lenvatinib. pERC reiterated that eligibility for treatment should align with the REFLECT trial inclusion criteria. For patients who have not progressed on sorafenib but are intolerant, pERC noted that it would be reasonable to consider switching to lenvatinib. Likewise, pERC supports consideration for switching from lenvatinib to sorafenib based on the clinical need of the patients provided progression has not occurred. pERC also acknowledged that it is reasonable to use second-line regorafenib after lenvatinib, given the similarity of mechanism of action of lenvatinib and sorafenib. pERC noted that the budget impact analysis (BIA) is sensitive to the number of patients eligible to be treated with lenvatinib, the extent of market expansion, the frequency of progression monitoring in clinical practice, and the dose intensity. Although the submitter's base-case BIA results project a cost-saving scenario, pERC recognized that the actual negotiated confidential price of sorafenib is likely lower than the price used in the BIA. Based on this, the budget impact of lenvatinib could be larger and no longer cost saving.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and BIA
- Guidance from the pCODR clinical and economic review panels
- Input from two patient advocacy groups (Canadian Cancer Survivor Network [CCSN] and Canadian Liver Foundation [CLF])
- Input from registered clinicians
- Input from pCODR's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, (Canadian Liver Foundation [CLF])
- One clinician group, (One joint input from six registered clinicians)
- The PAG
- The submitter (Eisai Limited)

The pERC Initial Recommendation was to recommend reimbursement of lenvatinib (Lenvima) for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC). Feedback on the pERC Initial Recommendation indicated that the manufacturer, patient advocacy group, and registered clinician group all agreed with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of lenvatinib on patient outcomes in the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC).

Studies included: Noninferiority study

The pCODR systematic review included one open-label, phase III, noninferiority (NI), randomized controlled trial (RCT) of lenvatinib versus sorafenib in first-line treatment of patients with advanced, unresectable HCC with no prior systemic therapy. A total of 954 patients were enrolled and randomized to lenvatinib (n = 478) or sorafenib (n = 476).

Patient populations: Select population

Key eligibility criteria included the following: histological or cytological confirmed diagnosis of unresectable HCC; pathologically confirmed or clinically confirmed diagnosis of HCC according to the American Association for the Study of Liver Diseases guidelines; cirrhosis of any etiology or with chronic hepatitis B or C infection, stage B (not applicable for transarterial chemoembolization [TACE]) or C based on the Barcelona Clinic Liver Cancer (BCLC) staging system, liver function status Child-Pugh score A, ECOG PS 0 or 1, adequate bone marrow, liver, renal, pancreatic; and blood coagulation function, adequately controlled blood pressure (< 150 mg Hg/90 mm Hg) with ≤ 1 antihypertensive medication, at least one measurable hepatic or non-hepatic target lesion by CT scan or MRI according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) and survival expectation of ≥ 12 weeks. Patients were excluded from the trial if they had any prior systemic anticancer therapy, including chemotherapy, sorafenib, investigational agents, and/or anticancer therapy (such as surgery, TACE, etc.) or blood enhancing treatment within 28 days before randomization. Allocation of treatment was stratified by region; macroscopic portal vein invasion, extrahepatic spread, or both (yes or no); ECOG PS (0 or 1); and bodyweight (< 60 kg or ≥ 60 kg).

Among 954 patients enrolled, baseline and disease characteristics were balanced between groups. The median age of patients was 63 and 62 years in the lenvatinib and sorafenib group, respectively. Patients were predominately male (84%), and from the Asia-Pacific region (67%). The majority of patients had an ECOG PS of 0 (63%), while 37% had an ECOG PS 1. Most patients had a Child-Pugh A liver function (99%); BCLC stage C disease (79%); bodyweight ≥ 60 kg (69%); and extrahepatic spread (61%). In both treatment arms, 43% of patients had one involved disease site, whereas 57% had two or more involved disease sites. Approximately one-third of participants were receiving concurrent systemic antiviral therapy for hepatitis B or C, and 70% had previous anticancer procedures.

Key efficacy results: Noninferior OS, improved progression-free survival, and OS

The key efficacy outcome deliberated on by pERC included OS, the primary end point. The REFLECT trial statistically demonstrated NI for OS of lenvatinib against sorafenib, with an upper limit of the CI that was below the NI margin of the trial, which was set at 1.08. Median OS was 13.6 and 12.3 months in the lenvatinib and sorafenib groups, respectively (HR: 0.92, 95% CI, 0.79 to 1.06). OS rate at six, 12, and 24 months was 80.8% versus 75.2%, 55.0% versus 50.0%, and 29.9% versus 26.2%, and in the lenvatinib versus sorafenib groups, respectively. Exploratory subgroup analyses of OS demonstrated consistent results across all subgroups.

Key secondary end points included PFS, time to progression (TTP), and ORR evaluated by investigator assessment using mRECIST for the primary analyses, all of which demonstrated statistical superiority of lenvatinib compared with sorafenib ($P < 0.0001$). The median PFS was double in the lenvatinib arm compared with the sorafenib arm at 7.4 versus 3.7 months, respectively. It is important to note the proportional hazards (PH) assumption was not met, which was confirmed by both visual inspection of the log-cumulative hazard plot and the PH global test. Given the study design is to demonstrate NI, the reviewers deemed this to be an acceptable violation of the assumption. Statistical superiority for PFS was demonstrated in most subgroups. TTP was statistically significant and approximately twice as long in the lenvatinib compared with sorafenib groups, at 8.9 months compared with 3.7 months, respectively (HR: 0.63; 95% CI, 053 to 0.73). ORR was also statistically significantly higher in the lenvatinib compared with sorafenib group (ORR: 24.1% versus 9.2%; respectively).

Patient-reported outcomes: No detriment in QoL

Patient-reported outcomes (PROs) were measured using the European Organization for Research and Treatment of Cancer (EORTC) questionnaires, the EORTC QoL Questionnaire C30 (EORTC QLQ-C30); the HCC-specific questionnaire, the EORTC QLQ-HCC18, and the EQ-5D scales. Study compliance was high (> 90%) for PROs throughout the study; however, due to the decline in patient numbers during the course of the study, interpretation was limited at later cycles. A clinically relevant change in score on any scale of the EORTC QLQ-C30 has been estimated to be a change of 10 points.

The overall median time to clinically significant worsening (TCW) of health-related QoL (HRQoL) (measured from baseline to the off-treatment visit) was similar between lenvatinib and sorafenib (1.7 months versus 1.8 months; respectively). There were no significant differences in TCW in most domains between the two arms. A clinically meaningful delay in deterioration for lenvatinib vs. sorafenib was observed for nutrition (4.1 versus 2.8 months, respectively) and body image (2.8 versus 1.9 months, respectively) from the EORTC QLQ-HCC18 domains. Based on EORTC QLQ-C30 domains, a clinically meaningful delay in deterioration for lenvatinib versus sorafenib was observed for role functioning (2.0 versus 1.9 months, respectively), pain (2.0 versus 1.8 months, respectively), and diarrhea (4.6 versus 2.7 months, respectively).

Based on the EQ-5D-3L, TCW was similar between lenvatinib and sorafenib (2.8 months versus 1.9 months) measured using the visual analogue scale (VAS). Using the health utility index measure of the EQ-5D-3L, nearly identical results were obtained for TCW in the lenvatinib and sorafenib arm (2.8 months and 1.9 months, respectively). Overall, pERC agreed that lenvatinib did not have a detrimental impact on patient's QoL.

Safety: Different and more manageable toxicity profile

A higher proportion of grade ≥ 3 TEAEs (75% versus 67%), treatment-related grade ≥ 3 TEAEs (57% versus 49%), serious TEAEs (43% versus 30%) and serious treatment-related TEAEs (18% versus 10%) occurred in the lenvatinib arm compared with the sorafenib arm, respectively. Adjusted by patient-years, the AE rate

was 18.9 episodes per patient-year in the lenvatinib group and 19.7 episodes per patient-year in the sorafenib arm.

The most commonly occurring (≥ 5%) grade ≥ 3 TEAEs in the lenvatinib group included hypertension (23%), decreased weight (8%), increased blood bilirubin (7%), proteinuria (6%), decreased platelet count (5%), and elevated aspartate aminotransferase (5%). In the sorafenib arm, the most common (≥ 5%) grade ≥ 3 TEAEs included hypertension (14%), palmar-plantar erythrodysesthesia (11%), elevated aspartate aminotransferase (8%), and increased blood bilirubin (5%). Treatment-related fatal AEs occurred in twice as many patients in the lenvatinib arm (n = 11) compared with the sorafenib arm (n = 4). In the lenvatinib arm, fatal AEs included hepatic failure (n = 3), cerebral hemorrhage (n = 3), and respiratory failure (n = 2); whereas, in the sorafenib arm tumour hemorrhage, ischemic stroke, respiratory failure, and sudden death (n = 1 for each) resulted in fatality.

pERC noted that the toxicity profile of lenvatinib is different from sorafenib. Although toxicities were more common with lenvatinib, the toxicities observed with lenvatinib (i.e., hypertension) are more easily managed than those seen with sorafenib (i.e., HFS) and would potentially cause less impact on a patient's quality of life.

Need and burden of illness: Poor prognosis and toxicities associated with available therapies

In 2017, there were approximately 2,500 new cases of HCC diagnosed in Canada. During the last two decades, the incidence of HCC (liver cancer) in Canada has increased by 3.1% per year in men, and 2.1% per year in women attributed in part to rising immigration from countries where risk factors for HCC such as hepatitis B and C are endemic. Other important risk factors for the development of HCC include alcohol use, hereditary hemochromatosis and aflatoxin exposure. The treatment approach for, and prognosis of, patients with HCC depends on the extent of the disease, hepatic functional reserve, and performance status. Child-Pugh class (A, B, or C) is the most commonly used metric to assess hepatic reserve. The prognosis for patients with untreated advanced and unresectable HCC is poor, with a median OS of less than one year. Sorafenib is currently approved and reimbursed across Canada for the first-line systemic treatment of patients with Child-Pugh class A advanced HCC. A number of newly approved agents have become available in the second-line setting including regorafenib and cabozantinib. pERC noted that a common and difficult to manage drug-related adverse event in the first-line setting with sorafenib treatment is HFS. This was reflected by input from patients, registered clinicians and the CGP. pERC therefore concluded that there is an unmet need in this setting for effective and more tolerable treatment options.

Registered clinician input: Preferable toxicity profile

Registered clinicians indicated that 40% to 50% of patients experience significant toxicities with sorafenib, with the major symptoms being HFS. These toxicities can be debilitating and negatively affect QoL. Clinicians see hypertension as more easily managed than HFS, which is more deleterious to a patient's day-to-day functioning. Patients with poorly controlled hypertension may however be better candidates for sorafenib. Generally, clinicians believe lenvatinib will be better tolerated than sorafenib.

Clinicians agreed that the inclusion/exclusion criteria of the REFLECT trial are reasonable and are in line with all current first- and second-line trials. Lenvatinib is seen as a reasonable choice for first-line patients and it may be suitable for patients who appear to have an intolerance to sorafenib. Patients would need to have maintained a Child-Pugh score of A and have no evidence of radiological progression before starting lenvatinib.

Clinicians remarked that there is no available data to suggest that current second-line therapies would be less effective following lenvatinib. As a result, they believe it would be reasonable to use regorafenib or cabozantinib after lenvatinib. Clinicians would use lenvatinib in patients with intermediate-stage HCC unable to receive TACE. They also noted that there is no evidence to generalize the REFLECT trial data in patients with Child-Pugh B liver function. It was suggested that lenvatinib should be considered for patients that one is trying to bridge to liver transplant where prolonged PFS is important. pERC, however, agreed with the CGP that there is no evidence to determine the utility of lenvatinib as a bridge to transplant.

PATIENT-BASED VALUES

Values of patients with hepatocellular carcinoma: Symptom and side effect control

Input was received from CCSN and CLF. A total of eight respondents provided input through CLF and five patients through CCSN, including three who had experience with lenvatinib. To further supplement the patient input, CLF has included a reference to a global survey of people living with HCC, conducted in 2016.

According to the global survey from 2016 of 256 patients living with HCC, CLF reported that fatigue had the biggest impact on QoL followed by abdominal pain and nausea. Other factors influencing QoL included appetite loss, weight loss, diarrhea, skin disorder, and alopecia. Patients with HCC also expressed deep mental and emotional impact such as fear, worry, shock, and sadness. Caregivers noted that living with patients with HCC impacted or seriously impacted their ability to work, travel, exercise, conduct household chores, spend time with family and friends, and fulfill family obligations.

Among the five patients providing input, CCSN noted that patients reported symptoms or problems they experienced with HCC that affected their day-to-day living and QoL as follows: living with uncertainty (80%), fatigue (60%), weight loss and/or lack of appetite (60%), pain (60%), not sleeping/restless (40%), stigma and judgment from others (20%), isolation or loneliness (20%) and anxiety, panic attacks and/or depression (20%).

Through the global survey, CLF noted that patients treated with sorafenib were more likely to rate their current QoL as poor. According to CCSN, five respondents reported that they were currently using lenvatinib (n = 3), chemotherapy (n=2), TACE (n = 2), radiation therapy (n = 1), surgery (n = 1), and liver transplant (n = 1). Four out of these five respondents reported that their needs in their current therapies are being acceptably met. Health care professionals who provided input noted that the most common side effects reported for patients were numbness, pain, or tingling in hands or feet, dry or peeling skin, skin redness, pruritus (skin itchiness), loss of appetite, diarrhea, weight loss, fatigue, weakness, and dry mouth.

A caregiver noted that the patient's most intolerable side effects were pruritus (skin itchiness), loss of appetite and numbness/pain/tingling in hands or feet. CLF also noted that both patients and caregivers felt that it was "very important" that patients have access to new treatments for unresectable HCC.

Patient values on treatment: Minimum impact on QoL, tolerable side effects

Health care professionals noted that the most common side effects with lenvatinib were high blood pressure, diarrhea, joint and muscle aches, decreased appetite and weight loss, stomatitis (mouth sores), headaches, and protein in the urine. The health care professionals also noted that the side effects were somewhat or very well tolerated by patients.

Among the three patient respondents in the CCSN survey who had experience with lenvatinib, one stated that lenvatinib had been the most effective while the other two patients rated lenvatinib as somewhat effective. CCSN also reported negative experiences from three patients who had experience using lenvatinib. These included minor diarrhea and possible cause for pain on foot soles, tongue inflammation, hypertension, fatigue, nausea and high blood pressure. Two of the respondents noted that diarrhea and high blood pressure were unacceptable side effects.

Overall patients value having access to new treatment options that improve survival, improve QoL, better manage side effects, and control disease. Patients and caregivers also value reduced burden on caregivers. Based on the results of the REFLECT trial, pERC agreed that lenvatinib aligns with the patient values of having additional treatment options that provide better management of side effects such as HFS and has no detrimental impact on QoL.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analyses

The EGP assessed cost-effectiveness and cost-utility analyses comparing lenvatinib to sorafenib for the first-line treatment of adult patients with advanced, unresectable HCC with no prior systemic therapy for disease.

Basis of the economic model: Clinical and cost inputs

Costs included drug acquisition costs, health state resource use costs, adverse events costs, monthly cost of treatment post-progression, cost of death, and wastage.

Key clinical effect estimates considered in the analysis include OS, utilities, dis-utilities, and adverse events. Although the REFLECT trial demonstrated noninferiority of lenvatinib and sorafenib, pERC noted that the submitted and EGP reanalysis estimates resulted in an incremental benefit in favour of lenvatinib.

Drug costs: Lower cost than sorafenib

Lenvatinib costs $8.1429 per mg. At the recommended dose of 8mg per day (< 60 kg bodyweight) or 12 mg per day (> 60 kg bodyweight), lenvatinib costs $97.7145 per day and $2,736.01 per 28-day course for the 12 mg/kg dose. At the 8 mg/kg dose, lenvatinib costs, $65.1430 per day and $1,824.01 per a 28-day course.

Sorafenib at its' listed price costs $46.4689 per 200mg tablet. At the recommended dose of 400 mg twice daily, sorafenib costs $185.84 per day and $5,203.52 per 28-day course. pERC noted that the negotiated confidential price of sorafenib is likely to be lower and will impact the ICER which could result in a non-dominant scenario.

Cost-effectiveness estimates: Lenvatinib more effective and less costly compared with list price of sorafenib

pERC deliberated upon the cost-effectiveness of lenvatinib versus sorafenib. pERC noted discussions from the EGP, indicating that the submitted model was well designed and robust. pERC noted that cost-effectiveness estimates provided by the submitter and EGP indicated that there was a potential incremental benefit associated with lenvatinib (0.22 and 0.30 QALY's, respectively). When this was combined with the lower price of lenvatinib, lenvatinib was dominant (more effective and less costly) in all scenarios. Based on the results of the REFLECT trial, pERC agreed that the efficacy of lenvatinib and sorafenib is likely similar while there appears to be differences in the toxicity profile.

pERC noted that the EGP made modifications to reflect 100% dose intensity and post-progression treatment received by patients. Although the trial dose intensity was used in the base case [87.5% (8 mg/kg) and 83.0% (12 mg/kg) for lenvatinib and 83% for sorafenib], the EGP increased these to 100%-dose intensity to account for potential drug wastage. The potential for drug wastage was identified in the PAG input which noted dose adjustments for lenvatinib may result in drug wastage and patient confusion if dose adjustments are made before finishing the capsules dispensed. Regarding post-progression therapies, an alternative scenario assumed that all patients who received post-progression therapy in the REFLECT trial (33% in the lenvatinib group and 39% in the sorafenib group) will receive regorafenib. This assumption was made in order to adjust for the extended OS that might be present in patients receiving post-progression treatments, and to balance their impact in both groups, lenvatinib and sorafenib. This impacted both costs and outcomes in favour of lenvatinib.

pERC further noted that the EGP's best estimates were based on the current list prices of lenvatinib and sorafenib. While pERC is unaware of the confidential price of sorafenib, pERC anticipates that the lower negotiated price will have an impact on the cost-effectiveness estimates. pERC concluded that the public drug plan cost of treatment with lenvatinib should not exceed the public drug plan cost of treatment with sorafenib.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Reimbursement population to align with REFLECT trial population, actual price of sorafenib will impact budget impact assumptions

pERC considered the feasibility of implementing a reimbursement recommendation for lenvatinib. pERC reiterated that eligibility for treatment should closely follow the REFLECT trial population. For patients who have not progressed on sorafenib but are intolerant, pERC agreed that it would be reasonable to switch to lenvatinib. Likewise, pERC supports switching from lenvatinib to sorafenib based on the clinical need of the patients, provided progression has not occurred. pERC also agreed that it is reasonable to use

second-line regorafenib after lenvatinib since lenvatinib and sorafenib have a fairly similar mechanism of action.

pERC discussed the budget impact of lenvatinib and noted that it is sensitive to the number of patients eligible to be treated with lenvatinib, the extent of market expansion, the frequency of progression monitoring in clinical practice, and the dose intensity. Although the submitter's base-case BIA results project a cost-saving scenario, pERC agreed that the actual negotiated confidential price of sorafenib is likely lower than the price used in the BIA. Based on this, the budget impact of lenvatinib could be larger and no longer cost saving.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Avram Denburg who was not present for the meeting
- Daryl Bell who did not vote due to his role as a patient member alternate

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of lenvatinib (Lenvima) for HCC, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
PAG is seeking clarity on the eligible patient population: • PAG noted that the trial included patients who are coinfected with hepatitis and is seeking confirmation that these patients would be eligible for treatment with lenvatinib. • In addition, whether patients with intermediate-stage HCC who are unable to receive TACE would be eligible for lenvatinib.	• pERC agreed that it is reasonable to include patients coinfected with hepatitis and patients with intermediate-stage HCC who are unable to receive TACE (provided they have Child-Pugh A liver function) in the reimbursement population. pERC noted that this was also supported by input from registered clinicians. Additionally, BCLC B patients were included in the study - which would include patients ineligible for TACE.
Time-limited basis: • Patients who are currently being treated with sorafenib • Patients who do not tolerate sorafenib and who have recently discontinued sorafenib due to intolerance	• For patients who have not progressed on sorafenib but are intolerant, pERC agreed that it would be reasonable to consider switching to lenvatinib. Likewise, for patients who have not progressed radiographically on lenvatinib but are lenvatinib intolerant, it would be reasonable to consider switching to sorafenib. pERC noted that this was also supported by input from registered clinicians.
Indication creep: • Child-Pugh score B (pivotal trial only included Child-Pugh score A) as well as to patients who have recently completed local regional therapy for HCC. • Clinicians may want to use lenvatinib to maintain any responses from local regional therapy or as a bridge to a liver transplant.	• The following patients were excluded from the trial, and thus the results cannot be generalized to these populations: pERC noted that patients with ECOG PS 2, Child-Pugh B liver function, ≥50% liver involvement, clear invasion of the bile duct or portal vein invasion at the main portal branch, brain metastases and liver transplantation were excluded from the REFLECT trial. pERC therefore does not support the generalizability of the trial results to these populations. • pERC noted that the REFLECT trial did not evaluate the efficacy of lenvatinib to maintain any responses from local regional therapy or its use as a bridge to transplant. pERC therefore does not support the generalizability of the trial results into these populations.
Sequencing and priority of treatments: • PAG is seeking guidance on the place in therapy for lenvatinib and which patient population would benefit most from the treatment and which patient population would be best suited for treatment with other available therapies (i.e., sorafenib). • PAG is seeking guidance on second-line treatments following lenvatinib, particularly given regorafenib is indicated after sorafenib and that the REFLECT trial is a noninferiority trial between lenvatinib and sorafenib. • There may be a preference in the first-line setting to use sorafenib as this would allow for a subsequent line of therapy with regorafenib.	• pERC noted that there is no evidence to help determine which patients may be better suited for lenvatinib or sorafenib treatment. pERC acknowledged that tolerability may be used to select patients (e.g., patients with uncontrolled hypertension may be better suited for sorafenib). pERC further agreed with the CGP that patients who meet the REFLECT trial criteria should be selected to receive lenvatinib while patients with who will be treated with sorafenib may include those with a Child-Pugh A liver function and either: ECOG PS 2, ≥ 50% of liver involvement, clear invasion of the bile duct or portal vein invasion at the main portal branch may qualify for treatment with sorafenib. • pERC agreed that there currently is no evidence to suggest that the efficacy of second-line HCC treatments would be influenced by the first-line therapy for these drugs with a fairly similar mechanism of action. While acknowledging the lack of evidence in this specific setting, pERC agreed that oncologists often extrapolate the efficacy of second line therapies after a new standard first line therapy is established across multiple tumor sites. pERC therefore supports the use of regorafenib after lenvatinib if clinically warranted. Furthermore, the CGP does not anticipate there will be a preference to use sorafenib upfront to ensure that patients can qualify for regorafenib or other second-line therapies.

BCLC = Barcelona Clinic Liver Cancer; CGP = clinical guidance panel; ECOG PS = eastern cooperative oncology group performance status; HCC = hepatocellular carcinoma; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; TACE = transarterial chemoembolization.