pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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: Cabozantinib (Cabometyx) **Submitted Reimbursement Request:** For the treatment of hepatocellular carcinoma (HCC) in adults after prior therapy.	
Submitted By: Ipsen Biopharmaceuticals Canada Inc.	**Manufactured By:** Ipsen Biopharmaceuticals Canada Inc.
NOC Date: November 8, 2019	**Submission Date:** October 16, 2019
Initial Recommendation: April 2, 2020	**Final Recommendation:** April 22, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	Cabozantinib (Cabometyx): Unit cost of $8,800 per pack of 30, 20 mg, 40 mg, and 60 mg tablets. At the recommended fixed dose of 60 mg per day, cabozantinib costs: $293.00 per day or $8,213.00 per 28-day cycle[a] [a] In the sponsor's submitted pharmacoeconomic model, the per day cost of cabozantinib is $250.80, based on a dose interruption adjustment.

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 conditionally recommends reimbursement of cabozantinib (Cabometyx) in adult patients with unresectable hepatocellular carcinoma (HCC) in the second-line setting after progression on sorafenib or lenvatinib if the following condition is met:

- Cost-effectiveness being improved to an acceptable level

Eligible patients should have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 and a Child-Pugh class status of A. Treatment with cabozantinib should continue until the patient no longer experiences clinical benefit or experiences unacceptable toxicity.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of cabozantinib compared with best supportive care (BSC) based on a clinically meaningful improvement in overall survival (OS), and progression-free survival (PFS) with no detriment to quality of life (QoL). pERC noted that cabozantinib is associated with increased but manageable toxicities. However, pERC was uncertain on how cabozantinib compared with regorafenib with regard to outcomes important to decision-making such as OS, PFS, and QoL due to a lack of robust direct or indirect comparative efficacy data.

	pERC also concluded that cabozantinib aligns with patient values in that it offers an improvement in OS, no detriment to QoL, and has manageable but not insignificant toxicities compared with BSC. pERC concluded that at the submitted price, cabozantinib could not be considered cost-effective compared with BSC. Additionally, pERC noted that there was considerable uncertainty in the cost-effectiveness estimates of cabozantinib compared with regorafenib due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit with cabozantinib compared to BSC and that the overall efficacy of cabozantinib compared with regorafenib is uncertain based on the available evidence, jurisdictions may want to consider alternate pricing arrangements and/or cost structures to improve cost-effectiveness to an acceptable level. **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 2019, approximately 3,000 new cases of hepatocellular carcinoma (HCC) were diagnosed in Canada. The treatment approach and prognosis of patients with advanced HCC depends on the extent of disease, hepatic functional reserve, and performance status (PS). The prognosis for patients with advanced, unresectable HCC with preserved hepatic reserve is poor with a median OS of less than one year. Sorafenib is currently approved and reimbursed in Canada for the first-line systemic treatment of patients with Child-Pugh A advanced HCC. Lenvatinib recently received a positive conditional recommendation for the treatment of first-line unresectable HCC. Regorafenib is available in the second-line setting for patients who have been previously treated with sorafenib. Progression-free survival (PFS) with second-line multitargeted tyrosine kinase inhibitors (TKIs) is approximately three months. Therefore, pERC agreed that there is a need for more effective therapies in the second-line setting that delay progression, prolong overall survival (OS) and improve quality of life (QoL).

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 phase III multi-centre, double-blind, placebo-controlled randomized control trial (RCT), CELESTIAL. The trial assessed the efficacy and safety of cabozantinib plus best supportive care (BSC) (hereafter referred to as cabozantinib) compared with placebo plus BSC (hereafter referred to as BSC) in patients with unresectable HCC with Child-Pugh A who had previously been treated with sorafenib. pERC noted that the requested reimbursement population was after prior therapy and was not specific to patients who had been previously treated with sorafenib. pERC considered that all patients in CELESTIAL had progressed on treatment with sorafenib, and that none of the patients had prior treatment with lenvatinib. pERC discussed that there was a statistically significant and clinically meaningful improvement in OS for patients treated with cabozantinib compared with BSC. pERC considered that although the median OS was reached in the cabozantinib group at the second interim analysis, and that the second interim analysis was determined to be the final analysis. pERC noted that the follow-up in the trial was relatively short. pERC also noted statistically significant and clinically meaningful improvements in PFS and objective response rate (ORR) in favour of cabozantinib compared with BSC. pERC discussed that QoL was an exploratory outcome in CELESTIAL and that overall, cabozantinib did not have a detrimental effect on patients' QoL compared with BSC. pERC also discussed that grade 3 to 4 adverse events (AEs) were higher in patients treated with cabozantinib compared with BSC. In addition, pERC noted that dose reductions and discontinuation of treatment for treatment-related AEs was higher in patients receiving cabozantinib compared with BSC. pERC considered that while the toxicities observed in patients receiving cabozantinib compared to BSC were significant, they agreed with the Clinical Guidance Panel (CGP) that the toxicities observed are expected with TKIs and are generally manageable.

pERC discussed the generalizability of the trial results and agreed with the CGP that patients eligible for treatment with cabozantinib should align with the inclusion criteria of CELESTIAL. Specifically, patients should have an ECOG of PS 0 to 1 and a Child-Pugh A liver function. pERC considered that the registered clinician group stated more studies would be required to assess the use of cabozantinib in patients with Child-Pugh B liver function or ECOG PS > 1. pERC also considered that sorafenib-intolerant patients were not specifically excluded from the trial and agreed with the CGP that these patients could be eligible for cabozantinib. However, pERC noted that patients who are intolerant to sorafenib would likely be switched to lenvatinib in the first-line setting. pERC also agreed with the CGP that there is currently no evidence to suggest that the efficacy of second-line HCC treatments would be influenced by the first-line therapy for drugs with a similar mechanism of action. Therefore, pERC agreed with the CGP that it would be reasonable for patients who progress on first-line treatment with sorafenib or lenvatinib to be eligible for second-line treatment with cabozantinib. pERC also noted that a very small number of patients (n = 6) received prior treatment with regorafenib in CELESTIAL. pERC agreed that there is currently minimal evidence to support the use of cabozantinib after treatment with regorafenib in the third-line setting, nor is there evidence to support the use of regorafenib after treatment with cabozantinib in the third-line setting. In the absence of evidence, pERC agreed that the optimal sequencing of TKIs is unknown. Overall, pERC concluded that there is a net clinical benefit of cabozantinib compared with BSC in HCC patients

with previous treatment with sorafenib or lenvatinib based on the clinically meaningful improvements in PFS, OS, an overall manageable toxicity profile, and no observed detriment in QoL.

pERC also discussed the results of the submitted indirect treatment comparison (ITC) that compared cabozantinib with regorafenib in the second-line setting. pERC noted that a matched adjusted indirect comparison (MAIC) was performed by the sponsor to derive comparative efficacy estimates for OS, PFS, and safety. pERC discussed that the pCODR Methods Team identified a number of limitations in the analysis that raised considerable uncertainty in the treatment estimates of cabozantinib compared with regorafenib. pERC noted that it was challenging to interpret the submitted data and that limited conclusions could be drawn from the MAIC. As a result, pERC was unable to draw a conclusion on the comparative effectiveness of cabozantinib compared with regorafenib in patients previously treated with sorafenib.

pERC deliberated upon input from one patient advocacy group. pERC noted that patients providing input did not have experience with cabozantinib and considered that the patient group expressed difficulty in finding HCC patients for the submission. pERC noted that patients with advanced HCC have a high disease burden and experience a number of disease-related symptoms and side effects with current treatment that affect their independence and QoL. pERC noted that patients desire control of symptoms and side effects including fatigue, hand and foot syndrome and diarrhea. pERC agreed that patients with advanced HCC value prolonged survival, control of symptoms and side effects and independence in pursuing daily activities in order to improve QoL. pERC discussed that AEs were higher in the cabozantinib group compared with BSC including fatigue, diarrhea, abdominal pain, ascites and hand and foot syndrome (palmar-plantar erythrodyaesthesia); however, pERC noted that these toxicities are manageable. Therefore, pERC concluded that cabozantinib aligns with patient values of prolonged survival, longer remission, manageable side effects, and no overall detriment to QoL.

pERC deliberated on the cost-effectiveness of cabozantinib compared with BSC and compared with regorafenib. pERC noted that there were two analyses submitted for the cabozantinib populations. The first compared cabozantinib with BSC in the previously treated with sorafenib-only population (which included the comparison of cabozantinib versus regorafenib) and the second compared cabozantinib with BSC in the second and third-line population (the full CELESTIAL trial population). pERC discussed the key limitations of the economic analyses including a short median follow-up in the CELESTIAL trial which required long-term OS extrapolation for the modelled 10-year time horizon, inappropriate cost discount for dose interruptions, and a lack of robust direct or indirect comparative efficacy data. Due to these limitations, there was high uncertainty in the magnitude of clinical benefit associated with cabozantinib. pERC noted that this made it challenging to estimate the incremental treatment effect of cabozantinib compared with BSC and compared with regorafenib. pERC concluded that cabozantinib, at the submitted price, was not cost-effective compared to BSC. pERC also noted that the cost-effectiveness of cabozantinib compared with regorafenib is uncertain because of the considerable uncertainty in the comparative effectiveness estimates in the submitted economic evaluation. pERC considered that since the drug price of cabozantinib was a key driver of the incremental cost-effectiveness estimates, a reduction in drug price would be required to improve cost-effectiveness to an acceptable level. pERC noted that longer follow-up study of clinical efficacy from CELESTIAL would help decrease the uncertainty in the incremental treatment effect and inform the true cost-effectiveness of cabozantinib.

pERC also discussed that the factors that most influence the budget impact include the number of patients that would receive cabozantinib and the comparators, the market share of cabozantinib and the comparators, and the acquisition costs of medications evaluated in the budget impact analysis (BIA). pERC noted that the submitted BIA estimated a small market share that may be due to the patient eligibility criteria in the CELESTIAL trial. pERC discussed that budget impact will increase if the number of eligible patients and the market share of cabozantinib increases.

pERC noted that the availability of 20 mg, 40 mg, and 60 mg tablets may facilitate dose reductions. However, pERC considered that there may be wastage of previously dispensed tablets of a higher strength. pERC agreed with PAG that although the availability of three different strengths is an enabler for ease of dose adjustments, pERC considered that if all tablet strengths are the same price, flat pricing would be a barrier as there would be added costs for dose modifications. The Committee also deliberated on the input from PAG, regarding factors related to currently funded treatments, the eligible population,

implementation factors, and sequencing, and priority of treatment. Refer to the summary table in Appendix 1 for more details.

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 budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group (Canadian Liver Foundation)
- input from registered clinicians: Cancer Care Ontario and a joint input from six registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Joint feedback on behalf of six registered clinicians and feedback from Cancer Care Ontario
- The PAG
- The sponsor [Ipsen Biopharmaceuticals Canada Inc.]

The pERC Initial Recommendation was to conditionally recommend reimbursement of cabozantinib (Cabometyx) in adult patients with unresectable hepatocellular carcinoma (HCC) in the second-line setting after progression on sorafenib or lenvatinib if the following condition is met:

- Cost-effectiveness being improved to an acceptable level

Feedback on the pERC Initial Recommendation indicated that the sponsor, registered clinicians, and PAG agreed with the Initial Recommendation. No feedback was received from the patient group.

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 cabozantinib (Cabometyx) for the treatment of adult patients with unresectable HCC after prior therapy.

Studies included: Phase III, Randomized, Double-Blind, Placebo-controlled Study (CELESTIAL)

The pCODR systematic review included one phase III randomized, double-blind, placebo-controlled study of cabozantinib in patients with advanced HCC who were previously treated with sorafenib. The CELESTIAL trial included a total of 707 patients who were randomized to receive cabozantinib (n = 470) plus BSC or placebo plus BSC (n = 237). The primary end point was OS. PFS and ORR were secondary end points, while health-related QoL and safety were exploratory end points considered.

Patient populations: Adult patients with HCC who had received prior sorafenib, ECOG PS 0 or 1 and Child-Pugh A

Key eligibility criteria included adults (age 18 and older) who had a histological or cytological diagnosis of HCC that is not amenable to a curative treatment approach, received prior sorafenib, and had progression following at least one prior systemic treatment for HCC. Sorafenib intolerance was not predefined in the trial. Additional eligibility criteria included: ECOG PS 0 or 1, Child-Pugh Score A, and adequate hematologic and renal function. All patients received sorafenib before receiving cabozantinib. There were

331 patients in the cabozantinib arm and 164 patients in the placebo arm that received only sorafenib as their previous treatment and were included in this analysis. There were 35 patients who received previous therapies in the first-line other than sorafenib in the cabozantinib group and 19 patients in the placebo group. In addition, 14 patients (3%) in the cabozantinib group and three patients (1%) in the placebo group received PD-1/PD-L1 therapies while 19 patients (4%) in the cabozantinib group and 12 patients (5%) of patients in the placebo group received prior TKI therapies other than sorafenib. Of these, six patients (1%) in the cabozantinib group and two patients in the placebo group (1%) received regorafenib. There was one patient in the placebo group and no patients in the cabozantinib group who received prior treatment with lenvatinib.

Key efficacy results: Statistically significant improvement in OS and PFS

The key efficacy outcome deliberated on by pERC included OS, PFS, and ORR.

OS: Median duration of OS was 10.2 versus 8.0 months in the cabozantinib and placebo groups respectively, an estimated 2.2-month difference in the medians. The median follow-up for OS was 22.9 months. The landmark estimate of the proportion of patients that were event-free at 12 months was 46% compared with 34% in the cabozantinib and placebo groups, respectively. The statistically significant (P = 0.005) hazard ratio (adjusted for stratification factors, disease etiology, geographic regions, and spread of extrahepatic disease) was 0.76 (95% CI, 0.63 to 0.92), suggesting that the risk of dying was smaller in the cabozantinib group, compared to the placebo group. The unadjusted hazard ratio (HR) was 0.77 (95% CI, 0.64 to 0.93), P = 0.0072.

PFS: The median duration of PFS was 5.2 months for those patients receiving cabozantinib versus 1.9 months for those receiving placebo. The HR (adjusted for stratification factors: disease etiology, geographic region and spread of extrahepatic disease) for PFS was 0.44 (95% CI, 0.36 to 0.52).

Sorafenib-Intolerant Patients from CELESTIAL (Post-Hoc Subgroup Analysis):
At the request of CADTH, the sponsor provided a post-hoc efficacy analysis for patients receiving cabozantinib based on prior treatment duration of treatment with sorafenib as sorafenib intolerance was not predefined in the CELESTIAL trial. To demonstrate the efficacy of cabozantinib for a potential sorafenib-intolerant population, the sponsor provided the median OS for patients based on the duration of treatment of less than three months with sorafenib. The median OS was 8.9 months in the cabozantinib group (n = 89) and 6.9 months in the placebo group (n = 47), HR of 0.72 (0.47 to 1.10). PFS was 3.8 months in the cabozantinib group versus 1.8 months in the placebo group with an HR of 0.35 (0.23 to 0.52).

ORR: In the cabozantinib group, n = 18 (4%) patients had a best overall response of Partial Response (PR) compared with n = 1 (0.6%) patients in the placebo group (P = 0.0059). The rate of stable disease in the cabozantinib group was higher than placebo (60% versus 33%).

Patient-reported outcomes: No clinically meaningful differences in QoL

Patients completed the EuroQoL 5D 5-level instrument (EQ-5D-5L) questionnaire at baseline, every four weeks until week 25, followed by every eight weeks until radiographic assessments discontinued. As well, a visual analogue scale (VAS), on which patients were to quantitate their health between 100 (“the best health you can imagine”) and 0 (“the worst health you can imagine”) was applied. An effect size for change from baseline equal to or greater than 0.3 was considered potentially clinically meaningful and the minimal important difference established in the literature was between 0.06 and 0.8 for EQ-Index and 7 for the EQ-VAS.

The EQ-5D-5L questionnaire completion was >85% in each treatment group until week 33, after which there were n < 20 of patients in the placebo group completed the questionnaire. The largest treatment difference post-baseline occurred at week five for mobility and usual activities; the effect size differences was in favour of placebo of 0.51 and 0.55 respectively, indicating a potentially clinically meaningful change from baseline.

At baseline, the mean EQ-Index scores were 0.792 in the cabozantinib group compared to 0.855 in the placebo group. At week 5, EQ-Index change from baseline was –0.117 in the cabozantinib group compared with –0.019 in the placebo group, favouring placebo. After which, the difference in mean change from baseline with respect to EQ-Index values were not considered clinically meaningful (< 0.06) through week

25 (beyond week 25, there were less than 20 patients in the placebo group).

At baseline, the mean EQ-VAS scores were similar among the two groups 73.5 in the cabozantinib group compared to 76.1 in the placebo group. The difference in mean change from baseline with respect to EQ-VAS values were not considered clinically meaningful (< 7) through week 33 (beyond week 33, there were less than 20 patients in the placebo group).

Limitations: Short trial follow-up; high-dose modifications for cabozantinib due to toxicity; QoL considered an exploratory analysis

Overall, CELESTIAL was a well-designed double-blind, placebo-controlled RCT.
There are some limitations that should be considered when interpreting the results of the trial affecting either external or internal validity. The trial had a relatively short follow-up period. Recruited patients were a selected group with Child-Pugh A and ECOG PS 0 or 1. Thus, cabozantinib was not investigated in patients with more advanced liver disease or poor PS. As well, the trial did not compare cabozantinib to active therapies of interest (i.e., no direct comparison to relevant active drugs such as regorafenib), therefore, direct comparative efficacy and safety data (cabozantinib compared to active therapies) were not available. There were high rates of dose modifications for toxicity in the cabozantinib group, with a median daily dose of 36 mg of cabozantinib, lower than in the starting dose of 60 mg. Although health-related QoL (HRQoL) was pre-specified in the protocol, results should be considered exploratory in nature since HRQoL analysis was not considered in the adjustment for multiplicity. There may be potential for confounding due to subsequent therapies, however the magnitude and direct of this effect are unknown.

Safety: Most Common Grade 3-4 AEs in ≥ 10% of patients were Palmar-Plantar Erthrosyaesthesia and Fatigue

Two dose reductions (in decrements of 20 mg cabozantinib or matched placebo) were allowed in the CELESTIAL trial for the management or prevention of worsening of an AE or toxicity. The median time to first-dose reduction was 38 days, and to first-dose interruption was 28 days. In the cabozantinib group, 57% of patients had first-dose reduction to 40 mg due to an AE, and 13% of patients on the placebo arm had a first-dose reduction to 40 mg due to an AE; 33% and 3.0% of patients, respectively, had a second dose reduction to 20 mg due to an AE; 38% of patients received 60 mg as their lowest dose, 29% received 40 mg, and 33% received 20 mg. The median average daily dose for the cabozantinib group was 35.8 mg, while the median average daily dose for the placebo group was 58.9 mg.

In the safety analysis population, there were 704 patients who received study treatment, 467 in the cabozantinib and 237 in the placebo group. The majority of patients in the trial experienced any grade AE, 99% (n = 460) of cabozantinib and 92% (n = 219) of placebo patients, respectively. The rate of discontinuation of treatment due to AEs that were considered to be related to treatment was 16% (n = 76) in the cabozantinib group and 3% (n = 7) in the placebo group. Any grade AEs that occurred at ≥ 10% were higher in the cabozantinib group compared to the placebo group. The most common AEs in ≥ 10% of patients leading to treatment discontinuation in patients in the cabozantinib group were palmar-plantar erythrodysaesthesia (n = 11, 2.4%), fatigue (n = 7,1.5%), decreased appetite (n = 5, 1.1%), diarrhea (n = 5, 1.1%), and nausea (n = 5, 1.1%). Approximately 82 (18%) of patients in the cabozantinib group and 14 (5.9%) of patients in the placebo group had treatment-related serious AEs. Grade 3 or 4 AEs were higher in the cabozantinib group 316 (68%) versus the placebo group 86 (36%). Serious AEs were more frequent in the cabozantinib group (50% versus 37%). Similarly, treatment-related serious AEs were more frequent in the cabozantinib group (18% versus 5.9%).

Death was slightly less frequent in the cabozantinib group (n = 317, 67%) versus placebo (n = 167, 70%) using the intention-to-treat population.

Comparator information: ITC of cabozantinib compared to regorafenib

PAG identified regorafenib as a relevant comparison and indicated interest in receiving data comparing cabozantinib with regorafenib. The sponsor submitted a MAIC to estimate the efficacy and safety of cabozantinib versus regorafenib in order to inform their cost-effectiveness model. The population in the MAIC is not representative of the entire requested reimbursement population: adults with hepatocellular carcinoma after prior therapy. The population in the MAIC does not include the entire CELESTIAL population, specifically it does not include patients with more than two prior therapies except for prior sorafenib, or third-line patients. Additionally, because sorafenib intolerance was not prespecified in the CELESTIAL trial, information pertaining to this population is uncertain. The MAIC evaluated the second-line population, after treatment with sorafenib. In their appraisal, the Review Team noted that there is a

lack of statistical comparison between the median OS and PFS estimates and as a result, any statements about the comparative effectiveness of the two drugs is not recommended. The MAIC is unanchored for the median OS and PFS. The unanchored approach assumes that all treatment effect modifiers and prognostic variable are accounted for. As well, there is insufficient information to understand what study design differences are unaccounted for and remain potential sources of bias in the MAIC. Other important outcomes identified such as health-related QoL, ORR, SAEs, WDAEs were not assessed in the MAIC. The Review Team noted that the proportional hazards assumption was not satisfied; therefore, it cannot be assumed that the hazard ratios are constant. Considering these limitations, the results of this MAIC should be interpreted with caution. An RCT comparing cabozantinib and regorafenib (in the same population) is required in order to determine the comparative efficacy of cabozantinib and regorafenib.

Need and burden of illness: Short Survival and Need for additional treatment options in the second-line setting

An estimated 3,000 new cases of HCC will be diagnosed in Canada in 2019, with a five-year OS rate of 19%. The intent of treatment for patients with HCC who have received prior therapy is palliative care. Median survival in the absence of treatment in this setting is less than eight months and PFS on second-line multitargeted TKIs is approximately three months. Therefore, QoL and toxicity are of utmost importance. Regorafenib is a second-line treatment available for patients with HCC who have tolerated treatment with sorafenib. Second-line treatment options have yet to be compared directly in adequately powered phase III trials.

Registered clinician input: Limited treatment options and unmet need

One joint input on behalf of two clinicians from Cancer Care Ontario and one joint input from a group of six clinicians was submitted for the review of cabozantinib for patients with HCC, who have been previously treated with sorafenib. Based on the results of the CELESTIAL trial, all clinicians agreed that cabozantinib is an effective treatment for patients with advanced HCC who have been previously treated with sorafenib. Clinician input expressed that cabozantinib may have a larger survival benefit compared to regorafenib, along with significantly longer progression-free PFS, and a similar adverse effect profile compared to other TKIs used in the HCC setting such as regorafenib and sorafenib. Sequencing options were presented by each clinician input based on currently available data and clinical opinion. Overall, the clinicians concluded that cabozantinib is a highly effective, emerging treatment that can fulfill a significant current unmet need for HCC patients. It is important to note that at the time of the initial input for cabozantinib was received regorafenib was pending pricing negotiation; however, as of November 2019, funding for regorafenib is available in some provinces.

PATIENT-BASED VALUES

Experience of patients with hepatocellular Carcinoma: Poor Prognosis and Limited Treatment Options

Patient input was provided by the Canadian Liver Foundation (CLF). The CLF provided insights from 45 liver cancer patients along with information from a 2016 global survey of 256 respondents of which none had direct experience with cabozantinib. The CLF noted that HCC prognosis is generally poor as the disease is often diagnosed at a later stage when it has significantly progressed, which limits treatment options. The current standard of first-line treatment for HCC patients is sorafenib, which has been associated with a poor QoL due to significant side effects. The CLF also noted that lenvatinib is a new systematic treatment that has been approved in Canada, but it is not yet available for reimbursement on all provincial formularies; therefore, patients who are able to access lenvatinib pay for it out of pocket. Regorafenib is a second-line treatment option for patients who have been treated with sorafenib; however, it is only reimbursed in a few Canadian provinces. A consistent theme emphasized throughout the patient input was the lack of access to treatments in Canada. The CLF concluded that due to poor prognosis of the disease and the limited treatment options, there is a need for new treatment options.

The CLF emphasized the difficulty of treating HCC, as it is usually an outcome of a pre-existing and progressive underlying liver disease. Patients may already be experiencing the effects of liver function impairment such as cirrhosis, hepatic encephalopathy and abdominal pain and swelling. Treatment depends on the stage and speed of the tumour growth, as well as the general health of the liver. The probability of cure usually decreases as the size of the tumour increases. In the global survey, approximately 80% of the patient respondents (205 out of 256) who were treated with sorafenib were more likely to rate their QoL as poor. For patients who have been on sorafenib, the only second-line treatment option is regorafenib which also has significant side effects such as hand-foot skin reactions, fatigue, diarrhea, and hypertension; however, the CLF noted that most of these side effects can be controlled by modifying the dose of the drug. The CLF commented that although regorafenib is not a cure, it fulfills a current unmet need for an additional second-line treatment for HCC in the palliative phase.

Patient values, experience on or expectations for treatment: Increased Survival and Control of Symptoms and Side Effects

The CLF patient input did not include patients who had experience with cabozantinib. However, patients value increased survival, and control of symptoms and side effects because HCC has a significant impact on the QoL of patients. Patients expressed a desire for a sufficient level of independence to allow them to continue with their daily activities. Specifically, one patient and one caregiver hoped that a new treatment would decrease the symptom of ascites which can improve their range of movement and other associated complications.

ECONOMIC EVALUATION

Cabozantinib is available in 20 mg, 40 mg, or 60 mg tablets. The unit cost of a pack of 30 cabozantinib tablets is $8,800.00, irrespective of the strength of the tablets in the pack. Based on recommended fixed dosing of 60 mg per day, the cost of cabozantinib is $8,213 per 28 days. As per the sponsor's submitted pharmacoeconomic model, the per day cost of cabozantinib is $250.80 is based on a dose interruption adjustment. Without the dose interruption adjustment, the cost of cabozantinib is $293 per day.

The sponsor provided a three-state partitioned-survival model to evaluate the cost-effectiveness of cabozantinib for patients with advanced hepatocellular carcinoma who have been previously treated with sorafenib. Two populations were evaluated in the submitted model. Patients previously treated with sorafenib only (subgroup of CELESTIAL trial) which included cabozantinib plus BSC versus BSC; and cabozantinib plus BSC versus regorafenib plus BSC. In addition, the second and third-line patients (all patients in CELESTIAL) included the cabozantinib plus BSC versus BSC alone comparison. The clinical data for the model is based on two main sources. For comparisons between cabozantinib and BSC, clinical input data were based on the CELESTIAL trial. For comparisons between cabozantinib and regorafenib, a MAIC was used to derive clinical data for the population of patients who received sorafenib as the only prior therapy.

For the cabozantinib plus BSC versus BSC alone comparison, the Economic Guidance Panel's (EGP's) best estimate of the incremental cost per quality-adjusted life-year (QALY) of cabozantinib compared to best supportive care ranges between $285,931 and $428,706. For the cabozantinib plus BSC versus regorafenib plus BSC, the EGP's best estimate of the incremental cost per QALY of cabozantinib compared to regorafenib ranges between $250,053 and $320,500. For the second and third-line population, which included all patients in the CELESTIAL trial, and compared cabozantinib plus BSC versus placebo plus BSC. The EGP's best estimate of the incremental cost per QALY of cabozantinib compared to BSC ranges between $302,298 and $442,810.

The overall structure and most assumptions in the model were considered appropriate. For the best-case scenario, the sponsor's chosen OS model (log logistic) is used by the EGP for their reanalysis. However, in the worst-case scenario, the alternate gamma model is used for the comparisons of cabozantinib plus BSC versus placebo plus BSC. CADTH identified the following key limitations of the sponsor's submitted economic analysis:

- A major limitation of the cost-effectiveness analysis between cabozantinib and regorafenib was the reliance on an indirect comparison to derive overall and PFS estimates. The MAIC used patient level data from the CELESTIAL trial for patients who received second-line treatment with prior sorafenib for the cabozantinib arm, and published data from the RESORCE trial for the regorafenib arm. This leads to high uncertainty around the incremental cost-effectiveness findings for the comparison of regorafenib versus cabozantinib in the pre-treated with sorafenib-only population.
- For the cabozantinib plus BSC comparison with both the placebo plus BSC and regorafenib plus BSC, a few assumptions favourable to cabozantinib influenced the estimation of incremental costs versus BSC and cabozantinib. These include discounting the cost of cabozantinib estimated by 14.5% to account for dose interruption and adjusting drug costs to assume drug discontinuation occurred at the midpoint of each monthly cycle. No adjustment was made for regorafenib. The sponsor said no adjustment was made for regorafenib as it was assumed that dose interruptions would occur during the week that regorafenib would be off treatment per four-week cycle. The CGP did not agree with the assumption that dose interruption would only affect the cabozantinib arm or that the 14.5% reduction in acquisition cost was appropriate as this would bias results in favour of cabozantinib.

The sorafenib-only population is not representative of the entire reimbursement request population. It is unclear whether sorafenib-intolerant patients were included as the CELESTIAL trial did not prespecify for sorafenib intolerance. Additionally, 3rd line patients were not included. The EGP made the following changes to account for the limitations in the sponsor's model, these included shortening the time horizon from 10 years to five years, removing the sponsor's adjustment for the monthly half cycle correction to the drug acquisition cost, using an alternative model (generalized gamma) for the OS curve used in the comparisons of cabozantinib and regorafenib, and the inclusion of drug wastage by assuming that 62% of

patients would have drug wastage based on the CELESTIAL trial where 62% of patients had dose interruptions while on cabozantinib.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Uncertain Market Share Assumptions
The factors that most influence the budget impact include the number of patients that would receive cabozantinib or their comparators, the market share of cabozantinib and its comparators, and the acquisition costs of medications evaluated in the BIA. In the base-case analysis, the sponsor applied the median time on treatment for cabozantinib based on the CELESTIAL trial and regorafenib based on the RESORCE trial to calculate medication budgetary costs. The EGP noted that it would be more appropriate to use the mean time on treatment to calculate medication costs as this better represents the full distribution of medication costs that will be incurred in the future. Additionally, the sponsor's market share of cabozantinib by year three was low; however, if the number of eligible patients and the market share increase, the budget impact will increase.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

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
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
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
- Dr. Christopher Longo who was not present for the discussion and deliberation for this review
- Dr. Maureen Trudeau who did not vote due to their role as the pERC Chair.

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 cabozantinib (Cabometyx) for HCC, through their declarations, none of the members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of the 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*. There was no non-disclosable information in this recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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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
Currently Funded Treatments • Sorafenib is the standard of care in first-line treatment of metastatic HCC and is funded in all provinces. • Lenvatinib recently received a conditional positive reimbursement recommendation for the first-line treatment of adult patients with unresectable HCC. As of February 1, 2020, it remains under provincial consideration in all provinces. • Regorafenib received a conditional positive reimbursement recommendation for treatment of HCC after sorafenib and is funded in some provinces. PAG is seeking data comparing cabozantinib with regorafenib. • The comparator in the CELESTIAL trial was BSC. This is a relevant comparator.	• pERC noted that lenvatinib is available in Canada for the first-line treatment of HCC and it is under consideration for provincial reimbursement. pERC agreed with the CGP that although the CELESTIAL trial did not include patients that had prior treatment with lenvatinib, there is currently no evidence to suggest that the efficacy of second-line HCC treatments would be influenced by the first-line therapy as these drugs have a fairly similar mechanism of action (e.g., sorafenib and lenvatinib) • pERC noted that there is a lack of statistical comparison between the median OS and PFS estimates of cabozantinib and regorafenib and as a result, pERC noted that the comparative effectiveness of cabozantinib and regorafenib is uncertain.

Eligible Patient Population
• PAG is seeking clarity on the eligible patient population.
  ○ PAG noted that sorafenib is funded for patients with advanced HCC not amenable to local therapy and who have an ECOG PS of 2 or less and Child-Pugh A liver function.
  ○ The reimbursement request from the sponsor does not specify Child-Pugh status and the CELESTIAL study enrolled patients with ECOG 0 or 1 and Child-Pugh A liver function.
  ○ PAG noted that the trial included patients who are co-infected with hepatitis B and C (HBV and HCV) and is seeking confirmation that these patients would be eligible for treatment with cabozantinib.
  ○ Patients in the CELESTIAL study had received prior sorafenib and PAG is seeking guidance on eligibility for cabozantinib for patients who had received other first-line treatments (e.g., lenvatinib) or were intolerant to sorafenib.
• There is a potential for indication creep to patients who had not received prior therapy (i.e., first-line treatment), particularly for patients who are intolerant to first-line sorafenib, as well as patients that were not included in the trial (e.g., patients with Child-Pugh B liver function and poor PS).
	• pERC agreed with the CGP that only patients with an ECOG PS of 0-1 should be eligible for cabozantinib as in the CELESTIAL trial. The CGP note that this primarily due to concerns around toxicity of treatment, for example fatigue, for patients with lower PS. pERC agreed with the registered clinicians that ongoing studies are needed for patients that have a poor ECOG performance status.
	• pERC agreed with the CGP that only patients with Child-Pugh A should be eligible as patients with Child-Pugh B status were excluded from the trial. pERC agreed with the registered clinicians that further studies are needed to determine the safety and efficacy of available treatments for HCC patients who have compromised liver function.
	• pERC agreed with the CGP that patients were stratified for etiological factor (HBV, with or without HCV, HCV without HBV). The CGP agree that the PFS subgroup analysis supports the use of cabozantinib for patients with HBV and/or HCV.
	• pERC agreed with the CGP and registered clinicians that the findings of the CELESTIAL trial are generalizable to patients who may be intolerant to sorafenib (although the trial did mandate that eligible patients had progressed on one prior therapy) or who may have progressed early on sorafenib since these patients were not specifically excluded, however, pERC noted that patients who are intolerant to sorafenib would likely be switched to lenvatinib in the first-line setting.

Implementation Factors • PAG is seeking information on the dose intensity	• pERC noted that two dose reductions (in decrements of 20 mg cabozantinib or matched

and the frequency of dose adjustments. • PAG is seeking clarity on treatment duration and criteria for treatment discontinuation as treatment with cabozantinib is recommended "until patient no longer experiences clinical benefit or experiences unacceptable toxicity." • PAG noted that cabozantinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair-time would be required. PAG identified the oral route of administration is an enabler to implementation. • However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program, and these programs can be associated with co-payments and deductibles that may cause financial burden on patients and their families.	placebo) were allowed in the CELESTIAL trial for the management or prevention of worsening of an AE or toxicity. • pERC noted that a high proportion of patients in both arms continued blinded treatment after radiological disease progression (32% in the cabozantinib and 49% in the placebo group). Blinded treatment after radiological disease progression could continue until a patient no longer experiences clinical benefit in the CELESTIAL trial. • pERC agreed with PAG that in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program, and these programs can be associated with co-payments and deductibles that may cause financial burden on patients and their families.
Sequencing and Priority of Treatments • PAG noted that some patients who have failed sorafenib may be receiving treatment with regorafenib. PAG is seeking information on the use of cabozantinib in third-line setting after regorafenib in second-line setting. • PAG is seeking whether there is information to guide sequencing of cabozantinib and regorafenib in patients who have failed first-line sorafenib. • PAG is also seeking guidance on the use of cabozantinib in the second-line setting following lenvatinib in the first-line setting.	• pERC agreed that there is minimal evidence to support the use of cabozantinib after treatment with regorafenib in the third-line setting. • pERC also noted that there is currently no evidence to support the use of regorafenib in the third-line setting after treatment with cabozantinib. The optimal sequencing of TKIs for HCC is unknown as the landscape is evolving.

BSC = best supportive care; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HBV = hepatitis B, HCC = unresectable hepatocellular carcinoma, HCV = hepatitis C, PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; TKI = tyrosine kinase inhibitors.